American Heart Journal

An international publication for the study of the circulation

VOLUME 61

JANUARY-JUNE, 1961

VOLUME 61

Printed in the United States of America

American Heart Journal

January, 1961, Volume 61, Number 1

Editorial

Negative (gas) contrast angiocardiography

Thomas M. Durant, M.D.
Philadelphia, Pa.

Venous angiocardiography using opaque contrast solutions (positive contrast) has been established as a valuable adjunct in cardiac diagnosis ever since the original studies by Castellanos and coworkers.[1] Most of the recent advances in this technique have been improvements in the solutions used or in the roentgen recording, including biplane stereoscopic visualization and high-speed cineradiography. A new technique developed recently, however, makes use of a gas (negative contrast) medium, or a combination of gas and an opaque medium (double contrast angiocardiography). This method, not designed by any means to replace older techniques, has been found, nevertheless, to have an important place in diagnosis, particularly in pericardial disease. Experimental work indicates, furthermore, that the sphere of clinical usefulness may be considerably extended in the not too distant future.

That a gas may be safely used as a contrast medium within the circulation will come as a surprise to many physicians who are well aware of the potential dangers of air embolism. It is indeed true that air, oxygen, or nitrogen may produce serious circulatory arrest and death when admitted inadvertently to vascular channels.[2] Other gases, notably carbon dioxide and nitrous oxide, however, are well tolerated in large amounts, without serious effects. The important difference between the former and latter, as far as embolism is concerned, is one of solubility. Carbon dioxide, for example, is at least twenty times as soluble in serum at 38.0°C. as is air or oxygen. This high solubility is responsible for the very rapid disappearance of bubbles from the circulation after injection, and is no doubt responsible for the excellent no-fatality record of the Rubin test for tubal insufflation in gynecologic examinations in which carbon dioxide is the gas routinely used. Teschendorf,[3] as early as 1951, had recognized the solubility factor and had recommended the use of either nitrous oxide or carbon dioxide for injections into the body cavity in order to avoid the danger of gas embolism.

During 1953-1954, while investigating roentgenologically in animals the mechanisms involved in circulatory arrest associated with intravenous injections of air, we were impressed by the excellent visualization of intracardiac structures provided by air.[4,5] Realizing that if such visualization could be safely achieved, a valuable diagnostic technique would become available, we studied, in dogs, the effects of injecting 7.5 c.c. of carbon dioxide per kilogram of body weight (a) intravenously, (b) into the left heart, and (c) into the peripheral end of the ligated carotid artery.[5] The consequent cardiovascular, respiratory, and chemical

Received for publication Aug. 16, 1960.

changes were minimal and lasted only seconds with any of these injections. By means of cinefluorographic technique the cardiac chambers, papillary muscles, valves, and great vessels were well visualized, and movements of the valve leaflets could be seen readily.

The first intravenous injections of carbon dioxide into human beings for the purpose of roentgen study were in anencephalic infants.[6] The dose was the same as that which had been used in animals (7.5 c.c. per kilogram). Brief respiratory disturbances were observed, as might be expected, but the injections were otherwise well tolerated. Excellent visualization of right heart structure and of the tricuspid ring were obtained roentgenologically. Since these original injections into human beings, approximately 80 adults have received doses of 50 to 100 c.c. intravenously at Temple University Medical Center. By comparison of body weight, this dose is only approximately one fifth of that given to dogs in our experiments, or to the two infants, and yet it has served well the purpose for which it was intended. It has not been used as yet for the demonstration of diseased valves, but the normal pulmonary valve has been well shown with doses of 100 c.c. One patient who had pulmonary emphysema with respiratory insufficiency received 50 c.c. without untoward effects.

The technique used routinely by Dr. Barbara Carter in our Roentgenology Department consists, first, in the establishment of a continuous intravenous drip via a three-way stopcock and a 20-gauge needle percutaneously in the left medial antecubital vein. For the demonstration of pericardial disease the patient is placed in the left lateral position so that the gas bubble, during its brief sojourn within the heart (approximately 15 seconds), will be in a superior location, adjacent to the endocardial surface of the right atrium and ventricle. The right lateral recumbent position is selected if visualization of the pulmonary valve is desired. Pure carbon dioxide is then thoroughly flushed several times through a 100-c.c. syringe, also via a three-way stopcock. This flushing may not be essential since, without it, the amount of air contamination could not be more than minimal, but it was established as a routine procedure early in our studies and does keep the safety factor in mind. It is important to emphasize that pure carbon dioxide is not the anesthetic mixture which contains only 10 per cent of this gas and which would be very dangerous. When these procedures have been performed, 50 to 100 c.c. of the pure carbon dioxide gas are injected rapidly into the vein via the stopcock of the intravenous apparatus. A roentgen exposure of the right heart border (factors: 85-100 kv., 400 Ma., 1/60 second) is made immediately after the injection, and is followed as rapidly as possible by a second exposure. The films are examined while wet, and the study is repeated if necessary. Cineflurorography may be used to follow continuously the movements of the right atrial wall, but this is not essential if not available, since much important information can be obtained without it. In patients who have a very much elevated venous pressure, 100 c.c. of gas are usually required since smaller amounts are likely to be trapped in the superior cava until solution occurs. When the study has been completed, the patient is kept in the left lateral position for a period of 10 minutes, or is turned into this position if the right lateral position was used for visualization of the pulmonary valve. This is another precaution which is probably not essential, but has been maintained as a routine procedure in order to avoid possible embolic effects.

The right heart wall (right atrium, pericardium, and pleura) normally measures 2 to 4 mm. in thickness and is convex laterally. When a pericardial effusion is present, it appears as added soft-tissue density between the bubble of carbon dioxide in the right atrium and the air-containing lung, thus increasing the thickness of the right heart border. In those patients who have a right-sided pleural effusion, the fluid within the pleura must be completely aspirated before the technique for pericardial visualization is used. It should be recognized that thickening of the mediastinal pleura or a mediastinal collection of fluid could appear as a pericardial abnormality, but such situations are infrequent in occurrence. Occasionally, gas in the right ventricle may appear to be in the right atrium, especially in a rotated heart, thus simulating an effusion in the pericar-

dium. A soft-tissue density along the caudal portion of the right heart border, due to a pericardial pad of fat or to the inferior vena cava, must not be confused. When constrictive pericardial disease involves the right wall of the heart, there will be straightening or angulation, and rigidity of the atrial border. Cineradiographic studies are particularly useful in the accurate evaluation of such alterations. Since pericardial disease, both effusive and constrictive, is so often difficult to diagnose by clinical and routine roentgen methods,[7] the additional information obtained by negative contrast study is often of vital importance.

In our experience the advantages of gas over opaque contrast angiocardiography are: (1) Pure carbon dioxide is safe; there is no danger of sensitivity, as with the various iodine-containing solutions now in use. (2) A venous cut-down is not necessary. (3) Carbon dioxide is not irritating to the vein. (4) No elaborate equipment is needed. (5) The gas is well tolerated and may be used in severely ill patients. (6) Repetition is possible without danger of excessive roentgen exposure. (7) There is no "streaming" due to poor mixing, as may occur with opaque media. It might be worthy of emphasis that the technique is one which may be used in small hospitals which do not have the usual angiocardiographic equipment.

The advantages, on the other hand, of opaque over gas contrast angiocardiography are: (1) A more extensive evaluation of the morphology and physiology of underlying heart disease is possible by the former technique. (2) Effusions loculated along the left heart border, anteriorly or posteriorly, cannot be detected with gas in the right atrium, but may be discerned with opaque contrast in other chambers. (3) Overlying structures which might be confused with thickening of the right atrial wall may be better delineated with opaque material.

It is quite possible that, with further investigation, the present disadvantages of gas contrast study may be overcome, and it is particularly likely that other advantages may be found. This is especially true of the demonstration of interatrial septal defects. Quite generally it is agreed that angiocardiography with opaque medium is largely unsuccessful in the diagnosis of this congenital lesion. Gas contrast and double contrast techniques, on the other hand, have readily demonstrated a surgically induced defect in dogs.[8,9] In these studies the carbon dioxide passed through the defect from right to left according to the principle of gas buoyancy. When the double contrast technique was used by Martin and associates,[9] with the animal in the prone position, the opaque medium was seen to pass through the heart chambers and pulmonary vessels in a normal fashion, whereas the gas dissociated from the dye-mixed blood and traversed the defect to the left atrium. The best results were obtained when the former medium was introduced slightly ahead of the carbon dioxide. A few attempts to demonstrate interatrial septal defects with gas in the human subject have failed in our clinic, but it is quite possible that relatively minor changes in technique, especially with respect to the position of the patient, will make possible an important advance in the diagnosis of this lesion.

The demonstration of left heart lesions by carbon dioxide in human beings remains for the future. Our own hesitation in using such a study has been due to the fact that, in animals injected with large amounts of the gas (7.5 c.c. directly into the left ventricle), a residual bubble may remain in the cavity of the heart for some minutes, and this bubble has been found to contain nitrogen and oxygen. The mixture is due to the diffusion of these other gases into the bubble of carbon dioxide according to the laws of gas equilibrium. Theoretically, this could lead to serious coronary embolism, but there has been no evidence of this or of any serious effects in our animals. If we can assure ourselves of the safety of this procedure, it may be possible to demonstrate the movements of the aortic leaflets, as we have been able to do cineradiographically in animal experiments. In the latter, we have been enabled to visualize also the coronary arteries very briefly, and no electrocardiographic or other evidence of harmful effect has been demonstrated even under these circumstances. On the other hand, we have been unable to visualize successfully the abdominal aorta when injections were made into that vessel.

Much remains to be done in the evaluation of this new technique, with or without

double contrast, in the visualization of various cardiac and vascular structures. Suffice it to say for the present, however, that a valuable method is now available for the diagnosis of many cases of pericardial disease in a safe and easy manner. We are gratified to note that other clinics in the United States and Germany[10,11] have confirmed our results and are using the method.

REFERENCES

1. Castellanos, A., Pereiras, P., and Garcia, A.: Arch. Soc. Estud. Clin. Habana **31**:523, 1937.
2. Durant, T. M., and Oppenheimer, M. J.: Med. Bull. Vet. Adm. MB-1, 7-16-57.
3. Teschendorf, W.: Acta radiol. **36**:297, 1951.
4. Durant, T. M., Oppenheimer, M. J., Lynch, P. R., Ascanio, G., and Webber, D.: Am. J. M. Sc. **227**:509, 1954.
5. Oppenheimer, M. J., Durant, T. M., Stauffer, H. M., Stewart, G. H., Lynch, P. R., and Berrera, F.: Am. J. Physiol. **186**:325, 1956.
6. Stauffer, H. M., Durant, T. M., and Oppenheimer, M. J.: Radiology **66**:686, 1956.
7. Durant, T. M.: Mod. Concepts Cardiovas. Dis. **27**:455, 1958.
8. Winters, W., Wilson, M., Chungcharoen, D., Stauffer, H. M., Durant, T. M., and Oppenheimer, M. J.: Am. J. Physiol. **195**:579, 1958.
9. Martin, J. F., Meredith, J. R., and Johnston, F. R.: Radiology **74**:947, 1960.
10. Grosse-Brockhoff, F., Koch, D., Logen, F., et al.: Fortschr. Geb. Röntgenstrahlen **86**:285, 1957.
11. Hoeffken, W.: Fortschr. Geb. Röntgenstrahlen **91**:1, 1959.

Clinical communications

Tolazoline hydrochloride (Priscoline) An effective pulmonary vasodilator

*Robert F. Grover, M.D., Ph.D.**
*John T. Reeves, M.D.***
*S. Gilbert Blount, Jr., M.D.****
Denver, Colo.

In the reduction of an elevated pulmonary vascular resistance, tolazoline hydrochloride has been reported to be effective by Dresdale and associates,[1] Gardiner,[2] Braun and associates,[3] and Wood[4]; Yu[5] found it to be of limited value and Rudolph and associates[6] concluded that tolazoline was not an effective drug in this respect. These divergent impressions are probably a consequence of differences in the pulmonary vascular condition of the patients being studied, as well as of variations in the technique of administering tolazoline. It will be demonstrated in this report that when tolazoline is administered in an effective manner to carefully selected patients, a most impressive reduction in pulmonary arterial pressure and pulmonary vascular resistance can be produced.[7] The circulatory effects of tolazoline in normal individuals when it is administered by this same technique will also be considered.

Materials and methods

Eight children with isolated ventricular septal defects, 6 of whom were less than 30 months of age, were selected to illustrate the pulmonary vasodilator properties of tolazoline. Selection was based on the presence of a pulmonary vascular resistance which was at least twice normal, and the reduction of this resistance to normal after tolazoline.

Tolazoline was administered in the same manner to 11 normal subjects who ranged in age from 6 to 45 years. Four had functional murmurs, 5 had minimal tuberculosis, 1 had a cardiac neurosis, and 1 was an ambulatory inpatient with questionable epilepsy. Clinical and laboratory examinations, including cardiac catheterization, indicated that each of these subjects was suitable for this investigation.

Catheterization of the right heart was performed under sedation with secobarbital in all cases, supplemented with meperidine in the young children. The brachial or femoral artery adjacent to the catheterized vein was intubated with a fine polyethylene tube in every patient. Pressures were obtained by means of Statham transducers energized with a Hathaway carrier amplifier system and were recorded photographi-

From the Cardiovascular Pulmonary Laboratory, Department of Medicine, University of Colorado School of Medicine, Denver, Colo.
Supported by Grant H-1208 from the National Heart Institute, U. S. Public Health Service.
Received for publication June 13, 1960.
*Assistant Director, Cardiovascular Pulmonary Laboratory; Instructor in Medicine, Department of Medicine, University of Colorado School of Medicine.
**Advanced Research Fellow of the American Heart Association, Cardiovascular Pulmonary Laboratory, University of Colorado Medical Center
***Head, Division of Cardiology; Professor of Medicine; Director, Cardiovascular Pulmonary Laboratory, Department of Medicine, University of Colorado School of Medicine.

Table I. Normal subjects. Hemodynamic changes after tolazoline

Patient data				Pressure (mm. Hg)		Heart rate	Saturation (% O_2)		Blood flow			Vascular resistance (dyne-sec.-cm.$^{-5}$-M.^{2})	
				PA	BA		PA	BA	A-V (vol.%)	O_2 (c.c.)	C.O. (L./min.)	TPR	TSR
L. W. 22.2 Kg.	M	6 yr. 0.84 M.^{2}	C	22/13(17)	100/68(78)	117	67.9	91.9	4.25	140	3.29	345	1,590
			T	18/10(14)	—	103	62.7	88.2	4.26	140	3.29	285	—
J. K. 24.8 Kg.	M	7 yr. 0.94 M.^{2}	C	20/10(13)	85/64(71)	118	67.2	93.6	4.13	135	3.27	300	1,630
			T	19/12(15)	89/57(69)	118	59.4	94.1	5.11	180	3.52	320	1,475
J. R. 38.7 Kg.	M	12 yr. 1.24 M.^{2}	C	25/13(18)	95/65(79)	86	67.4	92.8	4.83	180	3.73	480	2,100
			T	17/9 (11)	93/58(73)	78	73.3	96.7	4.41	190	4.31	260	1,680
J. V. 43.6 Kg.	F	15 yr. 1.36 M.^{2}	C	19/12(15)	101/65(83)	95	71.8	96.6	4.37	210	4.81	340	1,875
			T	17/8 (11)	86/55(69)	67	64.6	96.1	5.80	210	3.62	330	2,075
E. S. 46.2 Kg.	F	16 yr. 1.47 M.^{2}	C	28/14(19)	110/65(80)	62	77.1	99.3	4.17	175	4.20	530	2,240
			T	17/7 (12)	110/53(72)	90	79.8	97.0	3.26	205	6.79	235	1,345
B. A. 51.9 Kg.	F	24 yr. 1.50 M.^{2}	C	25/15(20)	108/59(75)	100	80.7	92.5	2.11	135	6.40	375	1,405
			T	24/8 (15)	118/60(79)	114	75.8	93.5	3.04	200	6.58	275	1,440
J. O. 58.5 Kg.	M	24 yr. 1.68 M.^{2}	C	16/8 (12)	118/68(85)	68	71.1	88.9	3.82	220	5.76	280	1,985
			T	20/8 (13)	117/65(82)	71	72.2	94.1	4.85	275	5.67	310	1,940
H. P. 55.2 Kg.	F	35 yr. 1.51 M.^{2}	C	21/9 (16)	96/56(69)	107	71.1	92.1	3.35	195	5.82	320	1,440
			T	18/8 (12)	106/60(75)	113	69.9	90.8	3.27	200	6.12	235	1,480
V. C. 62.3 Kg.	F	36 yr. 1.70 M.^{2}	C	27/13(18)	130/66(91)	66	70.5	92.1	3.80	200	5.26	475	2,350
			T	30/11(18)	128/65(83)	85	75.5	96.8	3.89	225	5.79	420	1,955
L. A. 54.0 Kg.	F	44 yr. 1.59 M.^{2}	C	22/8 (14)	96/54(68)	87	78.8	98.9	3.55	155	4.37	420	1,980
			T	22/10(14)	86/50(62)	135	81.4	98.4	3.00	180	6.00	295	1,315
R. M. 83.5 Kg.	M	45 yr. 2.05 M.^{2}	C	18/11(14)	112/76(88)	96	71.1	91.2	4.28	295	6.90	330	2,090
			T	21/12(15)	105/68(80)	93	71.6	85.3	2.91	265	9.11	270	1,440

Key to abbreviations. C: Control data. T: Values 10 minutes after tolazoline. Under "patient data," the initials indicate individual subjects. M: Male. F: Female. Kg.: Weight in kilograms. M.^{2}: Body surface area in square meters. PA: Pulmonary artery. BA: Brachial artery. Pressure expressed as systolic/diastolic (mean). Heart rate in beats per minute. A-V: Arteriovenous oxygen difference Vol. %: Cubic centimeters of oxygen per 100 c.c. of blood. O_2: Oxygen uptake in c.c. per minute. C. O.: Cardiac output. TPR: Total pulmonary resistance. TSR: Total systemic resistance.

cally with a Hathaway oscillograph. Mean pressures were determined by planimetry. Samples of blood were analyzed for their oxygen content and capacity by the method of Van Slyke and Neill. Oxygen capacity of blood was determined on each sample of systemic arterial blood, i.e., for each determination of the cardiac output. Oxygen uptake was calculated by collecting expired air, which was analyzed by the Scholander micromethod in duplicate. In small children, it was not feasible to collect expired air. Hence, oxygen uptake was estimated by means of a large body of data collected during a study of the metabolism of normal infants and children.[8] By means of height and weight, body surface area was determined from the charts of Sendroy and Cecchini.[9] A linear relationship was found between the mean values for oxygen uptake and body surface area: 172 c.c. per minute per square meter for girls, and 180 c.c. per minute per square meter for boys. It is of interest that Rudolph,[6] using independent data, arrived at a figure of 180 c.c. per minute per square meter.

Blood flow was calculated by application of the classic Fick principle. When systemic arterial desaturation (below 90 per cent) was found in patients who had a ventricular septal defect, a right-to-left shunt was assumed to be present. To calculate pulmonary blood flow in those cases, a pulmonary venous saturation of 92 per cent* was used.

Vascular resistance was calculated by dividing mean pressure by blood flow corrected for body size.[10] This tends to remove the effect of body size on oxygen uptake, thereby giving similar normal resistance values for adults as well as for small children.[11] This is convenient, and is helpful when the oxygen uptake is close to the basal metabolic rate, but the basic validity of such a correction remains to be established.[12]

A complete set of control data was obtained with the subjects at rest. Tolazoline hydrochloride, 1 mg. per kilogram diluted to about 5 c.c. for convenience, was then injected over 45 seconds through the cardiac catheter directly into the main pulmonary artery. Even though the duration of the injection can be prolonged to 2 minutes, any other major variation in time or dosage should probably be avoided. Promptly after the injection is completed, a cutaneous flush appears about the face and neck, and in blotchy areas over the rest of the body in some individuals. This is associated with a sense of warmth, and usually disappears after about 5 minutes. Later, there may be piloerection and a chilly sensation, and after 1 to 2 hours, nausea with vomiting are not uncommon.

*The rationale for this assumption will be presented in the discussion.

Systemic and pulmonary arterial pressures were recorded at minute intervals. After 10 minutes, allowing for stabilization of the circulation, cardiac output was again determined. In small children from whom expired air could not be collected, oxygen uptake was assumed to be unchanged* from that of the control state. When a ventricular septal defect was present, the catheter was promptly withdrawn to the right atrium, and a sample of blood was obtained there also.

Results

A. The hemodynamic effects of tolazoline in normal individuals. (See Table I.) The administration of a single moderate dose of tolazoline directly into the pulmonary artery in normal individuals had little effect on the mean pulmonary and systemic arterial pressures; it produced an average decrease of only 2 and 4 mm. Hg, respectively (Fig. 1,*A*). A mild tachycardia was usually observed (Fig. 1,*B*). The absence of systemic hypotension and the increase in heart rate have also been reported by other investigators.[13,14]

Tolazoline did not alter the cardiac output in the majority of these normal subjects (Fig. 2,*D*). Although the oxygen uptake tended to increase in these particular individuals (Fig. 2,*C*), statistical analysis of data from 35 subjects indicated a wide variation (S.D. ± 16 per cent), with no significant change (+8 per cent) in oxygen uptake after tolazoline. The change in the arteriovenous oxygen difference was also variable (Fig. 2,*A*). There was an increase in 4 individuals, a decrease in 4, and no change in 3. Since the pulmonary arterial saturation is related to the arteriovenous oxygen difference, the changes in this pa-

*The rationale for this assumption will be presented in the discussion.

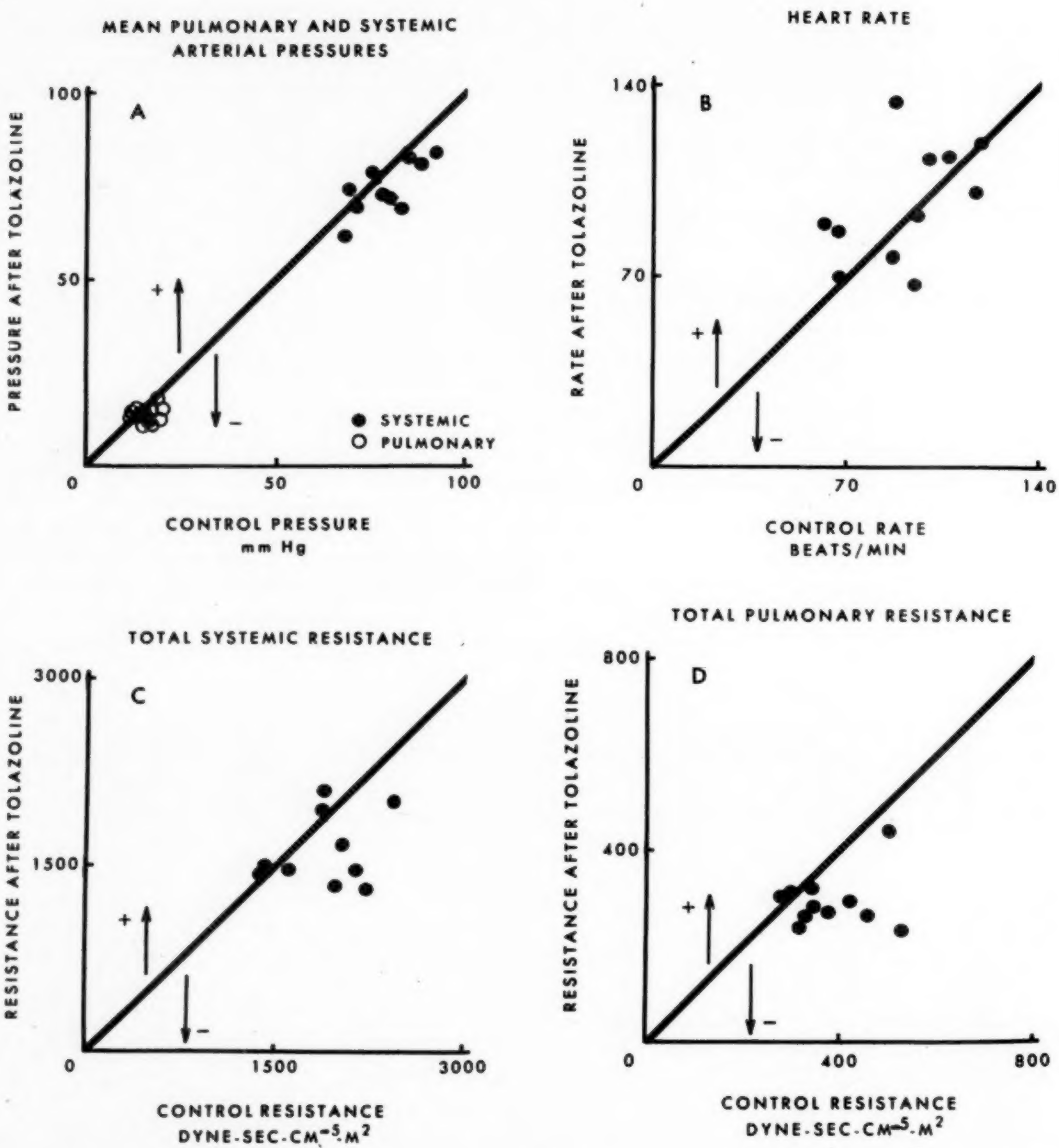

Fig. *1.* Effects of tolazoline on vascular resistance in 11 normal subjects. Values for blood pressure, heart rate, and vascular resistance 10 minutes after injection of tolazoline are plotted against control values to indicate patterns of change.

rameter after tolazoline were also variable (Fig. 2,*B*), but in no case was there a marked increase in saturation. This absence of consistent changes in either the arteriovenous oxygen difference or the oxygen uptake accounts for the usual lack of change in the cardiac output after tolazoline (Fig. 2,*D*). Horwitz,[14] using the ballistocardiograph, came to the same conclusion.

From these effects of tolazoline on pressure and flow, the resultant changes in systemic and pulmonary vascular resistances are illustrated in Fig. 1, *C* and *D*. There was an obvious reduction in resistance only in those cases in which an increase in cardiac output occurred. The effects of tolazoline on the pulmonary circulation of normal man have not been reported previously.

B. The hemodynamic effects of tolazoline in patients who have an increased pulmonary

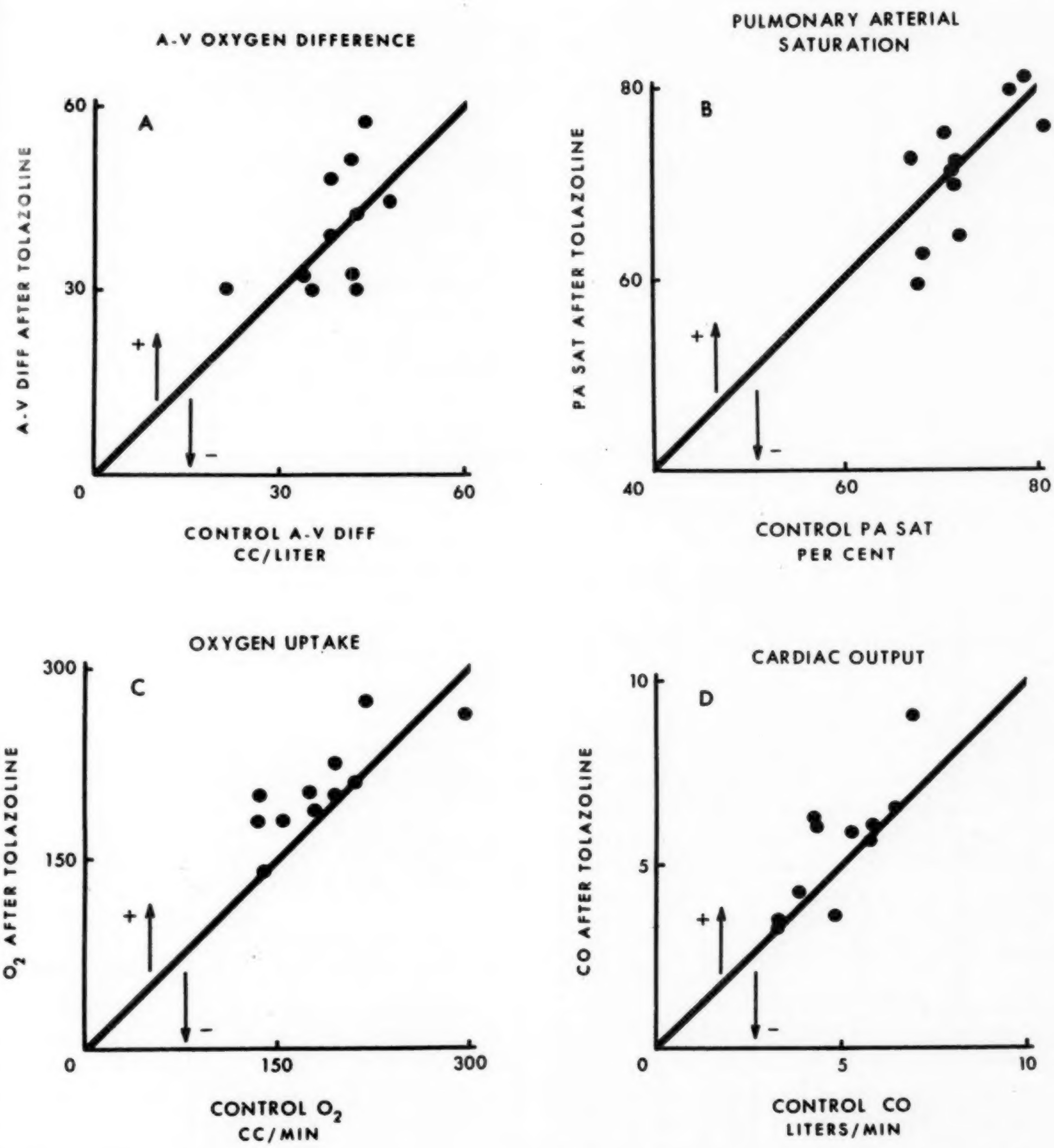

Fig. 2. Effects of tolazoline on cardiac output, as calculated by the Fick equation, in 11 normal subjects. Values 10 minutes after injection of tolazoline are plotted against control values to indicate patterns of change.

vascular resistance associated with ventricular septal defect. Marked pulmonary hypertension was present in every one of these 8 patients, with the pulmonary arterial pressure approaching systemic levels in 6 (Table II). Tolazoline reduced the pulmonary arterial pressure impressively in each case. An average reduction in mean pressure of 28 mm. Hg (Fig. 3) occurred promptly and was maintained for at least 20 minutes. This reduction in pulmonary arterial pressure was often in the presence of an increase, never a decrease, in pulmonary blood flow, due to an increase in shunting of blood from left to right through the ventricular septal defect.

Concurrently, tolazoline lowered the systemic arterial pressure, but to a lesser degree: the average reduction in mean pressure was only 9 mm. Hg. By contrast, this reduction in systemic pressure was usually associated with a decrease in systemic

Table II. Patients with ventricular septal defect. Hemodynamic changes after tolazoline

Patient data				Pressure (mm. Hg)			Saturation (% O_2)		Blood Flow					Vascular resistance (dyne-sec.-cm.$^{-5}$-M.^{2})		
									A-V O_2 difference (vol. %)		O_2 (c.c.)	Flow (L./min.)				
				PA	BA	W	PA	BA	Pul.	Syst.		Pul.	Syst.	TPR	TSR	TPR/TSR
M. E.	F	5 yr.	C	124/62(81)	116/68(84)	—	68.5	81.3	4.72	4.60	143	3.03	3.11	1,325	1,340	0.99
15 Kg.		0.62 M.^{2}	T	73/44(55)	98/57(71)	—	85.0	92.1	1.35	—	160	11.85	—	230	—	—
B. K.	M	10 mo.	C	82/56(66)	97/67(80)	5	61.9	83.3	4.39†	5.07	77*	1.75	1.52	1,295	1,805	0.72
8.3 Kg.		0.43 M.^{2}	T	56/12(30)	90/63(70)	—	73.5	86.1	3.08	5.33	77*	2.50	1.44	420	1,670	0.25
M. O.	M	5 mo.	C	102/47(68)	82/52(66)	—	67.9	82.9	3.63	6.96	48*	1.32	0.69	1,270	2,370	0.54
5.1 Kg.		0.31 M.^{2}	T	72/27(40)	78/53(62)	—	75.8	86.2	2.42	8.20	48*	1.98	0.59	500	2,630	0.19
R. T.	M	12 yr.	C	82/43(64)	98/62(74)	13	74.2	89.1	3.24	3.17	235	7.25	7.41	920	1,040	0.88
38 Kg.		1.30 M.^{2}	T	67/35(45)	74/52(59)	—	82.7	93.5	2.16	4.97	235	10.88	4.73	430	1,295	0.33
J. J.	M	14 mo.	C	96/48(67)	110/63(79)	—	75.8	95.1	2.94	3.82	81*	2.75	2.12	875	1,340	0.65
8.1 Kg.		0.45 M.^{2}	T	48/20(34)	102/52(69)	—	75.4	88.1	2.64	5.63	81*	3.07	1.44	395	1,725	0.25
P. M.	F	26 mo.	C	88/33(57)	116/62(83)	14	72.0	85.3	3.28	5.00	80*	2.44	1.60	860	1,905	0.45
9.3 Kg.		0.46 M.^{2}	T	43/25(32)	122/64(89)	—	74.0	86.9	2.75	5.20	80*	2.91	1.54	410	2,125	0.19
J. S.	F	30 mo.	C	116/62(78)	115/78(93)	15	80.2	86.1	2.29	5.94	95*	4.15	1.58	825	2,565	0.32
11.3 Kg.		0.55 M.^{2}	T	55/24(38)	113/58(78)	16	81.8	87.2	1.83	5.83	95*	5.19	1.63	320	2,110	0.15
M. H.	F	20 mo.	C	70/36(47)	76/40(52)	8	70.9	86.1	3.26	3.27	82*	2.52	2.51	715	785	0.91
9.8 Kg.		0.48 M.^{2}	T	44/13(30)	64/40(48)	7	79.3	85.0	2.08	3.95	82*	3.94	2.07	290	880	0.33

*Estimated.

†Patent foramen ovale; LA, 88.9 per cent.

Abbreviations are the same as for Table I. C: Control data. T: Values 10 minutes after tolazoline. BA: Brachial artery, or femoral artery in some cases. W: Wedge pressure, mean. Pul.: Pulmonary. Syst.: Systemic.

blood flow (Table II). Furthermore, a clear separation of pulmonary from systemic arterial pressure was often achieved (Fig. 4), whereas the two pressures were originally similar. Likewise, the ratio of pulmonary to systemic resistance, which was originally high, was reduced to normal after tolazoline (Table II). This illustrates the selective action of tolazoline on the pulmonary circulation in these patients.

Pulmonary blood flow was considerably increased in 6 patients and modestly increased in the other 2 after tolazoline (Table II). These increases in flow accompanied increases in pulmonary arterial saturation, resulting in a narrowing of the pulmonary arteriovenous oxygen differences.

When a decrease in pressure was combined with an increase in flow, a most impressive decrease in total pulmonary resistance was indicated (Fig. 5). In every case the total pulmonary resistance fell within the normal range after tolazoline, whereas the resistances were grossly elevated initially. It follows that the decrease in resistance was related to the initial level of resistance; the higher this resistance, the greater the decrease after tolazoline in these particular patients. Incidentally, this same principle applied to the normal subjects of this report.

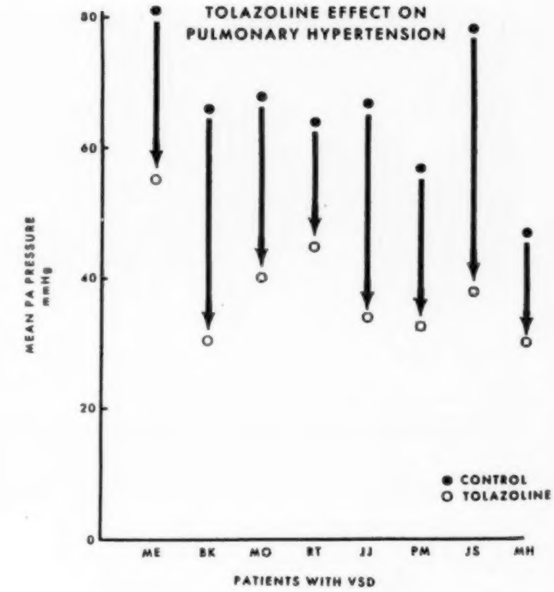

Fig. *3*. Reduction in pulmonary arterial pressures of 8 patients with ventricular septal defects and pulmonary hypertension who were given tolazoline.

Discussion

A. Pharmacology of tolazoline. In reviewing the subject of adrenergic blockade, Nickerson[15] presented the various mechanisms by which tolazoline could produce vasodilatation. Tolazoline will inhibit the pressor effects of epinephrine (adrenolytic action) as well as the vasoconstriction produced by simulation of sympathetic nerves (sympatholytic action). In addition, however, tolazoline will produce vasodilatation in the sympathectomized limb. Since this effect is not blocked by atropine, it is probably not a cholinergic effect (even though tolazoline has other powerful parasympathomimetic actions). This, then, is a direct, nonadrenergic relaxant action upon vascular smooth muscle, which is a very important factor in the vasodilatation produced in man.

Tolazoline produces the greatest vasodilatation in regions in which vasoconstriction is most marked.[13] This effect can be largely confined to a single extremity by injecting tolazoline slowly into the artery which supplies that extremity.[16] By analogy, tolazoline should be most effective in relieving pulmonary vasoconstriction when injected directly into the pulmonary artery.[1,2] These considerations underlie the method of administering tolazoline used in this investigation.

When tolazoline is injected intravenously in normal man, it does not produce generalized systemic vasodilatation. Rather, it produces a selective cutaneous dilatation,[17] with little effect upon the deeper resistance vessels of the systemic circulation. This accounts for the cutaneous flush and initial sense of warmth observed in most subjects. Subsequently, there tends to be a loss of body heat, and the increased metabolic rate (oxygen uptake) observed in some individuals is probably a compensatory mechanism which maintains body temperature. The reported decrease in blood sugar[18,19] may be related to the increased metabolic rate, or simply another manifestation of the adrenolytic action of tolazoline.

Tolazoline increases the heart rate in man and in many other animals through a direct stimulating action on the heart, and

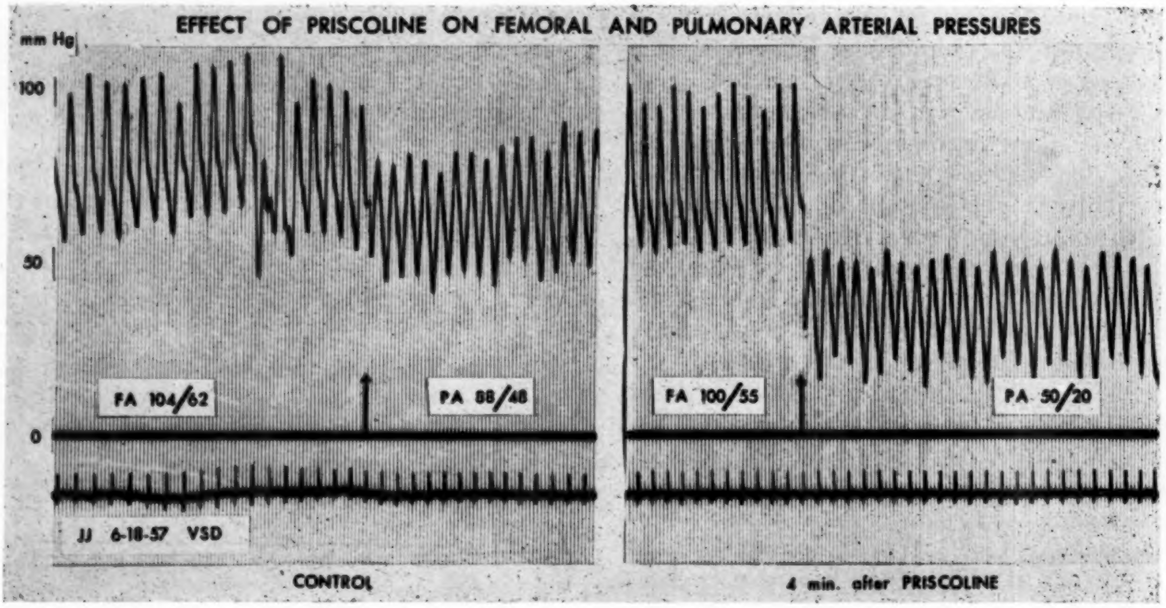

Fig. *4*. Pressure tracings from Patient J. J., who had a ventricular septal defect and marked pulmonary hypertension. The single recording system was switched from the femoral artery to the pulmonary artery by turning a stopcock, at the point indicated by the arrow. The two pressures which were originally of similar magnitude are clearly separated after tolazoline.

independent of the autonomic nervous system. Although this action does not increase the cardiac output in normal man receiving therapeutic doses of tolazoline (Fig. 2,*D*), larger doses in the isolated heart do increase cardiac output.[20]

Tolazoline rivals histamine as a powerful stimulant of the gastrointestinal tract, increasing salivary, gastric, and pancreatic secretions. This accounts for the delayed nausea and vomiting which may follow the administration of tolazoline. These are parasympathomimetic effects which can be blocked with atropine.

B. Pulmonary circulatory effects of tolazoline. Undisputable was the marked fall in pulmonary arterial pressure after the administration of tolazoline in the 8 patients of this report who had pulmonary hypertension and a ventricular septal defect (Fig. 3). The pulmonary arterial wedge pressure, when obtained, was normal and did not change (Table II). The normality of the wedge pressure in patients who have an uncomplicated ventricular septal defect has been well documented by Kjellberg.[21] Hence, the observed decrease in pulmonary arterial pressure indicates a similar reduction in the pressure *gradient* across the pulmonary vascular bed.

An increase in pulmonary blood flow accompanied the fall in pulmonary arterial pressure. This flow was calculated from the oxygen uptake and the pulmonary venous and pulmonary arterial oxygen saturations. In certain cases, only the pulmonary arterial oxygen content and saturation could be determined directly, and the other two factors had to be estimated on the basis of two assumptions: (1) the oxygen saturation of pulmonary venous blood was normal and remained constant; and (2) the oxygen uptake was not altered by tolazoline in those children in whom it could not be measured. Pulmonary venous blood was assumed to be 92 per cent saturated in those patients who had right-to-left shunts. This is a slightly lower figure than the normal arterial oxygen saturation of 94 per cent reported from this laboratory (elevation 5,300 feet).[22] Because of the possibility of hypoventilation in the sedated infants, or of venous admixture[21,23,24] in these patients with an increased pulmonary blood flow, the value of 92 per cent was selected as a compromise. Calculations based on a higher saturation would give higher resistance values, but the difference would be consistent in a given individual. It is reasonable to assume that the pulmo-

nary venous saturation did not change after tolazoline, since there was no consistent change in the arterial saturation of the 11 normal subjects.

Although there is a tendency for the oxygen uptake to increase after tolazoline (Fig. 2,*C*), this did not prove to be a statistically significant increase when a larger body of data was examined. Hence, when oxygen uptake had to be estimated, it was assumed that the uptake remained unchanged after tolazoline. This is a conservative assumption, since an actual increase in oxygen uptake would further lower the pulmonary vascular resistance after tolazoline.

The pulmonary arterial oxygen saturation increased in most cases and remained unchanged in the others after the administration of tolazoline. When pulmonary blood flow is calculated from estimates based on the foregoing assumptions, it follows that an increase in pulmonary arterial saturation due to tolazoline is in itself presumptive evidence of an increase in pulmonary blood flow.

It has been established that the pressure gradient across the pulmonary vascular bed in these 8 patients was decreased after tolazoline in the face of a constant or increased pulmonary blood flow. Consequently, the calculated pulmonary vascular resistance was greatly decreased in every patient. In all probability, this means an increase in the total cross-sectional area of the pulmonary vascular bed, i.e., vasodilatation. Since right atrial pressure did not change, intrathoracic pressure was also presumably constant. Furthermore, the hemoglobin concentration was neither high nor variable in any of these patients, so that changes in the viscosity of the blood are unlikely. The decrease in pulmonary arterial pressure implies a decrease in the transmural pressure of the pulmonary arteries. If the degree of vascular tone remained constant, this would lead to a decrease in the caliber of the vessels. Since the converse, vasodilatation, apparently occurred, a marked decrease in pulmonary vascular tone after tolazoline is indicated.

C. Interpretation of results. The 8 patients reported upon were carefully selected from a much larger series. Two criteria were used in this selection: first, the total pulmonary

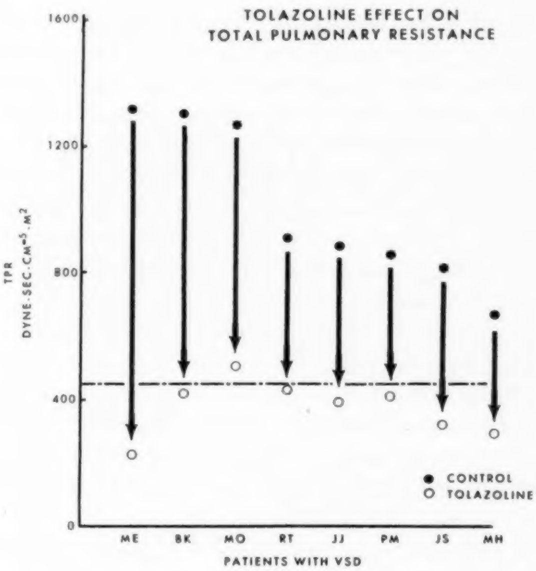

Fig. 5. Reduction in elevated total pulmonary resistances of 8 patients with ventricular septal defects who were given tolazoline. The dashed line indicates the approximate upper limit of normal.

resistance was initially high, being at least twice normal; and second, the resistance was reduced to normal after tolazoline i.e., there was a gross decrease in resistance of more than 50 per cent in every patient. Obviously, then, patients who exhibited the most noticeable response were deliberately selected to establish beyond question that, under the proper circumstances, tolazoline is a most effective pulmonary vasodilator.

Tolazoline is just as effective in young children when the pulmonary vascular resistance is increased to a lesser degree than it was in the 8 patients reported upon here. In older children, tolazoline may not reduce an elevated resistance to normal, even though there is a distinct pulmonary vascular response. When a patient with congenital heart disease has had a very high pulmonary vascular resistance for years, his pulmonary vascular bed usually becomes refractory to tolazoline.

We believe that a vasodilator such as tolazoline will be most effective in those patients in whom the pulmonary vascular resistance is increased primarily as a consequence of generalized constriction of hypertrophied small muscular arteries. When this smooth muscle is relaxed, vasodilation can occur. This responsive situation is

found most frequently in the first years of life, as illustrated by the patients in this report. When pulmonary hypertension has been present for years, obliterative changes, such as intimal proliferation and fibrosis, thrombosis, and atherosclerosis, are found in the smaller pulmonary arteries. When these lesions are widespread, accounting for a large portion of the increased pulmonary vascular resistance, a vasodilator could not be expected to lower the resistance appreciably. However, both the magnitude and the duration of the increased pulmonary vascular resistance are probably important in determining the age at which a given patient will lose his responsiveness to tolazoline.

Tolazoline is potentially capable of reducing an elevated pulmonary vascular resistance whenever the increased resistance results from pulmonary vasoconstriction. Although this report has been confined to patients who had isolated ventricular septal defects, equally impressive results have also been obtained in patients who had other congenital cardiovascular defects. When the increase in pulmonary vascular resistance is associated with hypoxia, either acutely or, e.g., in chronic pulmonary emphysema, tolazoline has also been found to lower the resistance.

Summary

Eight infants and young children who had ventricular septal defects and high pulmonary vascular resistances were carefully selected to illustrate the pulmonary vasodilator effects of tolazoline. In each of these 8 patients, tolazoline produced a marked reduction in pulmonary hypertension (average decrease, 28 mm. Hg) and an impressive decrease in pulmonary vascular resistance (over 50 per cent) to normal levels. The effects of tolazoline on the cardiovascular dynamics of 11 normal subjects were also examined and found to be minimal. When tolazoline is delivered directly into the pulmonary artery in a dose of 1 mg. per kilogram over 45 seconds, it is highly effective in relieving pulmonary vasoconstriction.

REFERENCES

1. Dresdale, D. T., Michtom, R. J., and Schultz, M.: Recent studies in primary pulmonary hypertension, including pharmacodynamic observations on pulmonary vascular resistance, Bull. New York Acad. Med. **30**:195, 1954.
2. Gardiner, J. M.: The effect of "Priscol" in pulmonary hypertension, Australasian Ann. Med. **3**:59, 1954.
3. Braun, K., Izak, G., and Rosenberg, S. Z.: Pulmonary arterial pressure after Priscoline in mitral stenosis, Brit. Heart J. **19**:217, 1957.
4. Wood, P.: Pulmonary hypertension, with special reference to the vasoconstrictive factor, Brit. Heart J. **20**:557, 1958.
5. Yu, P. N.: Primary pulmonary hypertension: report of six cases and review of literature, Ann. Int. Med. **49**:1138, 1958.
6. Rudolph, A. M., Paul, M. H., Sommer, L. S., and Nadas, A. S.: Effects of tolazoline hydrochloride (Priscoline) on circulatory dynamics of patients with pulmonary hypertension, Am. Heart J. **55**:424, 1958.
7. Grover, R. F., Bowes, W. A., Jr., and Blount, S. G., Jr.: Pulmonary hypertension relieved by Priscoline in patients with congenital heart disease, Clin. Res. **6**:85, 1958.
8. Lee, V. A., and Iliff, A.: The energy metabolism of infants and young children during postprandial sleep, Pediatrics **18**:739, 1956.
9. Sendroy, J., Jr., and Cecchini, L. P.: Determination of human body surface area from height and weight, J. Appl. Physiol. **7**:1, 1954.
10. Bazett, H. C., Cotton, F. S., Laplace, L. B., and Scott, J. C.: The calculation of cardiac output and effective peripheral resistance from blood pressure measurements, with an appendix on the size of the aorta in man, Am. J. Physiol. **113**:312, 1935.
11. Hamilton, W. F.: Regulation of arterial pressure. *In* Howell's Textbook of Physiology, ed. 15, Philadelphia, 1947, W. B. Saunders Company, p. 711.
12. Reeves, J. T., Grover, R. F., Filley, G. F., and Blount, S. G., Jr.: Cardiac output in normal resting man, J. Appl. Physiol. (In press.)
13. Wakim, H. G., Peters, G. A., and Horton, B. T.: The effects of a new sympatholytic drug (Priscol) on the peripheral circulation in man, J. Lab. & Clin. Med. **35**:50, 1950.
14. Horwitz, O., Montgomery, H., Longaker, E. W., and Sayen, A.: Effects of vasodilator drugs and other procedures on digital cutaneous blood flow, cardiac output, blood pressure, pulse rate, body temperature, and metabolic rate, Am. J. M. Sc. **218**:669, 1949.
15. Nickerson, M.: The pharmacology of adrenergic blockade, Pharmacol. Rev. **1**:27, 1949.
16. Prandoni, A. G., and Moser, M.: Clinical appraisal of intra-arterial Priscoline therapy in the management of peripheral arterial diseases, Circulation **9**:73, 1954.
17. Rottenstein, H., Horwitz, O., Montgomery, H., Sayen, A., and Siems, L. L.: The vasodilator effects of Priscoline in patients with ischemic extremities, Am. J. M. Sc. **221**:661, 1951.
18. Sherif, M. A. F., Razzak, M. A., and Hassaballah, A. M.: Comparative study of some imidazoline derivatives and dihydrogenated ergot alkaloids on blood sugar and gastric

acidity, Arch. internat. pharmacodyn. **110**:1, 1957.
19. Janes, R. G.: Certain metabolic effects of niacin and Priscoline, Am. J. Physiol. **174**:46, 1957.
20. Ahlquist, R. P., Huggins, R. A., and Woodbury, R. A.: The pharmacology of benzyl-imidazoline (Priscol), J. Pharmacol. & Exper. Therap. **89**:271, 1947.
21. Kjellberg, S. R., Mannheimer, E., Rudhe, U., and Jonsson, B.: Diagnosis of Congenital Heart Disease. ed. 2, Chicago, 1959, Year Book Publishers, Inc., p. 372.
22. Anderson, L. L., Willcox, M. L., Silliman, J., and Blount, S. G., Jr.: The pulmonary physiology of normal individuals living at an altitude of one mile, J. Clin. Invest. **32**:490, 1953.
23. Ordway, N. K.: Studies in congenital cardiovascular disease. IV. Impaired pulmonary diffusion of oxygen in persons with left-to-right shunts, Yale J. Biol. & Med. **24**:292, 1952.
24. Wood, P.: Pulmonary hypertension, Brit. M. Bull. **8**:348, 1952.

The management of resistant fluid-retention states with intravenous L-arginine monohydrochloride in combination with mercurial diuretics

*David A. Ogden, M.D.**
*Lawrence Scherr, M.D.***
*Norton Spritz, M.D.****
*Albert L. Rubin, M.D.*****
E. Hugh Luckey, M.D.
New York, N. Y.

In patients with resistant edema the production of hyperchloremic acidosis is an effective method for restoring responsiveness to mercurial diuretics.[1] Calcium or ammonium chloride, and, more recently, L-lysine monohydrochloride, have been used successfully for this purpose.[1-3] The presence of nausea, vomiting, gastritis, acute peptic ulcer,[4] or an abnormal state of consciousness may make the oral use of these medications inadvisable or impossible. In such instances a safe intravenous agent capable of producing adequate hyperchloremic acidosis would be of value.

The effects of the calcium ion preclude the intravenous administration of large amounts of calcium chloride. Intravenous ammonium chloride produces severe side effects,[5] particularly in patients with Laennec's or cardiac cirrhosis.[6-8] Lysine monohydrochloride is not yet available for parenteral administration. On the basis of its role in the Krebs-Hanseleit urea cycle, L-arginine monohydrochloride has been administered intravenously in large doses to patients with liver disease,[9-11] suggesting that this agent could be safely used in patients with resistant edema.

It was therefore administered intravenously to a group of patients with mercurial-resistant edema, thus producing hyperchloremic acidosis and restoring mercurial responsiveness.

Materials and methods

Five hospitalized patients with edema which was accompanied or unaccompanied by ascites due to either chronic congestive heart failure or Laennec's cirrhosis were selected for study. The diagnosis was clearly established by history, physical examination, and appropriate clinical and laboratory tests. Throughout the study the patients were treated with bed rest, 2-Gm. salt diet, fluid restriction to 1,200 to 1,500 c.c. per day, and digitalis when

From the Cardiorenal Laboratory of the Second (Cornell) Medical Division, Bellevue Hospital, the Medical Service of the Veterans Administration Hospital, New York, N. Y., and the Department of Medicine, Cornell University Medical College, New York, N. Y.
This work was supported in part by grants from the New York Heart Association, the U. S. Public Health Service (H-2054 C), the American Heart Association, and Lederle Laboratories.
Received for publication May 27, 1960.
*Research Fellow of the American College of Physicians.
**Research Fellow of the New York Heart Association.
***Established Investigator of the Health Research Council of the City of New York.
****Established Investigator of the American Heart Association.

indicated. During the control period, each patient received mercurial diuretics and 2 received a spirolactone, but all failed to respond with significant loss of weight. Distress attributed to marked retention of fluid made diuresis important or imperative. The presence of nausea and vomiting, acute gastritis, or abnormal states of mentation precluded the use of oral agents capable of producing adequate hyperchloremic acidosis.

A 500-c.c. intravenous infusion which contained 42.13 Gm. of L-arginine monohydrochloride* and provided 200 mEq. of chloride ion was administered daily over a period of 2 to 4 hours. When the desired effect had been produced (see below), daily intramuscular injections of meralluride (70 mg.), administered as Mercuhydrin (2 ml.), were begun, continuing the daily administration of L-arginine monohydrochloride in the dosage described. Intake of fluids, including the 500-c.c. infusion, was limited to 1,200 to 1,500 c.c. a day.

Daily body weight, 24-hour urine volume, and electrolyte concentrations, as well as frequent determinations of plasma electrolytes and venous blood pH were obtained throughout the study. Sodium and potassium were determined with a Baird atomic flame photometer, using an internal lithium standard, and chloride was determined by the method of Schales and Schales as modified by Summerson. Carbon-dioxide combining power was measured with a Thomas–Van Slyke manometric apparatus, and venous blood pH with a Cambridge research pH meter, using a temperature correction of 0.0147 for each degree centigrade to correct to body temperature. Blood urea nitrogen was measured by the Summerson modification of the Van Slyke and Cullen method.

Results

Table I presents measurements of plasma and urine electrolytes and body weight in each patient during: (1) the control period preceding the administration of L-arginine monohydrochloride; (2) production of hyperchloremic acidosis with L-arginine monohydrochloride; and (3) during daily mercurial injection with continued administration of L-arginine monohydrochloride.

Control period. The lack of significant loss of weight during this period reflects the resistance of these patients to mercurials and to the other diuretics employed. Concentrations of urinary sodium or chloride greater than 10 mEq. per liter, observed in several of the patients during this period, represent an effect of the diuretics used; these diuretics, however, were clinically ineffective. The short control period in Patient W. P. was dictated by the urgent need for diuresis.

Production of hyperchloremic acidosis with L-arginine monohydrochloride. The daily parenteral administration of 42.13 Gm. of L-arginine monohydrochloride alone (200 mEq. of chloride ion) for 1 to 3 days consistently produced a rise in the concentration of chloride in urine and plasma, as well as a fall in carbon-dioxide combining power and in venous pH, when the latter was determined. Loss of weight did not occur during this period.

On the basis of previous experience in this laboratory, a significant increase in urinary chloride is one of the best indications that response to mercurial agents may ensue.[2]

Mercurial administration after the production of hyperchloremic acidosis. Daily mercurial injections and the continued daily administration of L-arginine monohydrochloride after the production of hyperchloremic acidosis resulted in significant natriuresis, diuresis, and loss of weight in each patient. The average weight lost per patient was 17.0 pounds, or 3.3 pounds per day during this period.

Plasma chloride, carbon-dioxide combining power, and venous blood pH returned toward normal during the diuresis. The administration of potassium chloride in amounts determined by the measured 24-hour excretion of potassium prevented the development of hypokalemia.

In all but one patient was it possible to maintain the diuresis until adequate clinical response had been achieved. In Patient J. M. the diuresis gradually diminished and it was necessary to discontinue the mercurial agent. Subsequent production of hyperchloremic acidosis by

*Kindly supplied by Cutter Laboratories, Berkeley, Calif.

Table I. *L-arginine monohydrochloride*

Diagnosis	*Cirrhosis of the liver*						*Congestive heart failure*			
Patient	*J. M.*		*R. T.*		*W. P.*		*P. P.*		*E. K.*	
Control Period Days	10		15		1		4		3	
Weight change (lb.)	+2½		−3		−½		+4½		−¼	
Urine sodium, in mEq. L. (average)	3		13		15		3		12	
Urine chloride, in mEq. L. (average)	54		15		18		4		23	
Plasma chloride, in mEq. L. (average)	97		98		88		107		95	
CO_2 combining power, in mM. L. (average)	21.9		27.1		31.8		26.7		24.3	
Venous blood pH (average)	7.34		7.44		7.46		———		7.44	
Arginine Alone Days	1		2		2		1		3	
Weight change (lb.)	0		0		0		0		−3	
Urine sodium, in mEq. L. (average)	1		5		31		3		5	
Urine chloride, in mEq. L. (average)	134		66		48		21		18	
Urine chloride* (mEq./L.)	85	134	14	100	18	57	4	21	9	32
Plasma chloride, in mEq./L. (average)	106		101		98		———		106	

*The two figures are the values obtained immediately prior to and after that period of treatment.

the same method then restored mercurial responsiveness.

Side effects. No side effects related to L-arginine monohydrochloride were encountered. Hyperpnea due to acidosis did not occur. Despite evidence of hepatic insufficiency in most of the patients studied, signs of hepatic encephalopathy did not develop in any instance during the study. Alterations in the hemogram or urinalysis attributable to the use of L-arginine monohydrochloride were not observed. Several of the patients developed a transient rise in blood urea nitrogen during treatment with L-arginine, but the blood urea nitrogen returned to pretreatment levels at the conclusion of therapy.

Discussion

The monohydrochloride salt of L-arginine has a molecular weight of 210, and therefore contains 4.76 mEq. of the acid amino-acid radical and of chloride ion per gram. Amounts of this agent similar to those used in this study have been rapidly administered parenterally to a large number of patients for the purpose of evaluating its efficacy in the management of hepatic encephalopathy.[9-11] Its effectiveness in this condition is controversial, but untoward effects in patients with hepatic insufficiency or in normal subjects have not been observed. Parenteral L-arginine monohydrochloride is, therefore, a particularly suitable agent for producing hyperchloremic acidosis in

Table I. *L-arginine monohydrochloride*—Cont'd

Diagnosis	*Cirrhosis of the liver*						*Congestive heart failure*			
Patient	*J. M.*		*R. T.*		*W. P.*		*P. P.*		*E. K.*	
Arginine Alone—Cont'd Plasma chloride* (mEq./L.)	99	106	98	107	88	98	—	——	88	116
CO_2 combining power* (mM./L.)	21.2	18.0	26.2	19.8	28.6	17.6	—	——	24.8	14.0
Venous blood pH*	7.36	7.30	7.46	7.28	7.46	7.32	—	——	7.44	7.25
Arginine With Mercuhydrin Days	7		7		6		3		3	
Weight change (lb.)	−13		−17		−17		−16		−22	
Urine sodium, in mEq./L. (average)	33		55		73		74		67	
Urine chloride, in mEq./L. (average)	128		145		85		124		107	
Urine chloride* (mEq./L.)	134	94	100	131	57	92	21	115	32	103
Plasma chloride, in mEq./L. (average)	103		105		100		105		106	
Plasma chloride* (mEq./L.)	106	98	107	99	98	90	—	100	116	99
CO_2 combining power* (mM./L.)	18.0	18.5	19.8	24.6	17.6	22.3	—	24.3	14.0	20.2
Venous blood pH*	7.30	7.39	7.28	7.48	7.32	7.38	—	7.34	7.25	7.40

*The two figures are the values obtained immediately prior to and after that period of treatment.

patients with retention of fluid secondary to hepatic cirrhosis, or to congestive heart failure with its concomitant hepatic insufficiency.[12-14]

The production of a hyperchloremic acidosis to induce mercurial responsiveness should be limited to those patients who do not respond to salt restriction, bed rest, digitalis when indicated, oral diuretics, and initial mercurial therapy. When indicated, oral agents may be successfully used to produce this metabolic state in most instances. The use of parenteral L-arginine monohydrochloride for this purpose should be restricted to patients who cannot take oral medications, or in whom there is a specific contraindication to the use of the available oral medications. Therapy with this agent must be attended by careful clinical observation and laboratory control to avoid symptomatic metabolic acidosis, and should be carried out only in hospitalized patients.

Summary

The daily intravenous administration of a large dose of L-arginine monohydrochloride is a safe and effective method of producing hyperchloremic acidosis and restoring responsiveness to mercurial diuretics in patients with refractory retention of fluid due to hepatic cirrhosis or congestive heart failure. Results obtained with 5 patients thus treated, and the advantages of this agent in certain clinical situations, are discussed.

REFERENCES

1. Rubin, A. L., Thompson, H. G., Jr., Braveman, W. S., and Luckey, E. H.: The management of refractory edema in heart failure, Ann. Int. Med. **42**:358, 1955.
2. Hollister, J. H., Lubash, G. D., Cohen, B. D., Braveman, W. S., Rubin, A. L., and Luckey, E. H.: Refractory edema treated with calcium chloride in combination with mercurial diuretics, Am. Heart J. **56**:629, 1958.
3. Rubin, A. L., Spritz, N., Mead, A. W., Herrmann, R. A., Braveman, W. S., and Luckey, E. H.: The use of L-lysine monohydrochloride in combination with mercurial diuretics in the treatment of refractory fluid retention states, Circulation **21**:332, 1960.
4. Sackler, A. M., and Sophian, L. H.: The effects of the ingestion of amino acid on gastric secretion, with particular reference to L-lysine monohydrochloride, Am. J. Clin. Path. **28**:258, 1957.
5. Stauffer, J. C., and Scribner, B. H.: Ammonia intoxication during treatment of alkalosis in a patient with normal liver function, Am. J. Med. **23**:990, 1957.
6. Phillips, G. B., Schwartz, R., Gabuzda, G. J., Jr., and Davidson, C. S.: The syndrome of impending hepatic coma in patients with cirrhosis of the liver given certain nitrogenous substances, New England J. Med. **247**:239, 1952.
7. Bessman, A. N., and Evans, J. M.: The blood ammonia in congestive heart failure, Am. Heart J. **50**:715, 1955.
8. Sievers, M. L., and Vander, J. B.: Toxic effects of ammonium chloride in cardiac, renal and hepatic disease, J.A.M.A. **161**:410, 1956.
9. Fazekas, J. F., Ticktin, H. E., and Shea, J. G.: Effects of L-arginine on hepatic encephalopathy, Am. J. M. Sc. **234**:462, 1957.
10. Reynolds, T. B., Redeker, A. G., and Davis, P.: A controlled study of the effects of L-arginine on hepatic encephalopathy, Am. J. Med. **25**:359, 1958.
11. Fahey, J. L., Nathans, D., and Rairigh, D.: Effect of L-arginine on elevated blood ammonia levels in man, Am. J. Med. **23**:860, 1957.
12. Koletsky, S., and Barnebee, J. H.: "Cardiac" or congestive cirrhosis: pathologic and clinical aspects, Am. J. M. Sc. **207**:421, 1944.
13. Felder, L., Mund, A., and Parker, J. G.: Liver function tests in chronic congestive heart failure, Circulation **2**:286, 1950.
14. Evans, J. M., Zimmerman, H. J., Wilmer, J. G., Thomas, L. T., and Ethridge, C. B.: Altered liver function of chronic congestive heart failure, Am. J. Med. **13**:704, 1952.

Cardiac output in systemic arteriovenous fistulas complicated by heart failure

*Otto M. Spurny, M.D.**
*John A. Pierce, M.D.***
Little Rock, Ark.

Congestive heart failure is recognized as a complication of systemic arteriovenous fistulas, although it is not seen commonly in clinical practice. The development of this complication is related to the size and duration of the fistula. Although many patients with simple systemic arteriovenous fistulas have been studied, surprisingly few measurements of the cardiac output have been reported in these patients during heart failure. The purpose of this report is to present the cases of 3 patients with traumatic arteriovenous fistulas in whom the cardiac output was measured during a period of cardiac decompensation. Certain hemodynamic considerations are discussed.

Case reports

Case 1. A 52-year-old retired railroad worker (#14-37-22) was admitted on Nov. 8, 1957, complaining of shortness of breath which had persisted for 3 weeks. He had noted the gradual appearance of bilateral pedal edema and had gained 25 pounds in weight. Prior to admission he developed both dyspnea at rest and orthopnea. The patient described a gunshot wound in the left thigh from a .25 caliber pistol in 1924. In 1936, he developed a weeping dermatitis on the lower part of his left leg, and chronic edema appeared in this region. He was hospitalized on three occasions for treatment of varicose veins and was retired from railroad service in 1954, because of this disability. Since then he has been able to do only part-time labor.

On physical examination, the blood pressure was 120/80 mm. Hg, the pulse rate was 88 per minute, and the veins in the neck were distended. There were scattered râles over both lung bases. The heart was enlarged, but no significant murmurs were heard. The liver was palpable 8 cm. below the right costal margin. A pulsatile mass, which measured approximately 8 by 8 cm., was present in the left lower quadrant of the abdomen. In the lower third of the left thigh a thrill was felt and a continuous murmur was heard. There was moderate pitting edema of both legs, more marked on the left. The skin over the lower part of the left leg was thickened and indurated.

Antecubital venous pressure was 260 mm. of saline, and the circulation time (arm to tongue, Decholin) was 18 seconds. A roentgenogram of the chest showed marked cardiomegaly and an effusion in the right pleural cavity. An electrocardiogram revealed a normal sinus rhythm and left axis deviation. In Lead V_5 the onset of the intrinsicoid deflection was 0.05 second after the onset of ventricular depolarization. The T waves were deeply inverted in Leads I, aV_L, and V_2 through V_6. In Lead V_6 the negative T wave was 0.9 mv. in amplitude.

The patient was treated with digitalis, mercurial diuretics, and a diet restricted to 250 mg. of sodium daily. He lost 10 pounds in the first 10 days of hospitalization. Table I presents the results obtained at cardiac catheterization on the sixth hospital day. On the twenty-first hospital day, repair was made of a fistula which measured 24 mm. in diameter at the point of arteriovenous communication. Recovery from the operation was uneventful. The results of a second cardiac catheterization, performed 10 days after this operation, are also presented in Table I. Subsequently, an aneurysm of the left iliac artery was excised and an end-to-end

From the Department of Medicine, University of Arkansas Medical Center, Little Rock, Ark.
Received for publication May 31, 1960.
*Instructor in Medicine.
**Assistant Professor of Medicine, and Investigator for the Arkansas Heart Association.

anastomosis was performed. The patient again recovered without incident. Six months later he was admitted because of intestinal obstruction. At this time no evidence of congestive heart failure was noted, and a roentgenogram of the chest did not reveal cardiomegaly.

COMMENTS. This patient had an arteriovenous fistula for 33 years before congestive heart failure occurred. At the time of operation the fistula was large and was associated with an aneurysm of the iliac artery. Signs of regional venous insufficiency appeared 12 years after the time of the original injury and led to his early retirement 3 years before operation. The significance of the electrocardiographic findings is difficult to assess, since the possibility of coronary atherosclerosis cannot be excluded completely. These changes were not diagnostic of myocardial infarction, however, and are ascribed to ischemia associated with congestive heart failure. The primary cause of his congestive failure was almost certainly the increased work incident to his increased cardiac output. The extremely long period of time between injury and the appearance of heart failure has been described previously.

Case 2. A 57-year-old man (#16-03-51) was admitted on Dec. 11, 1958, because of progressive exertional dyspnea and orthopnea which had been present for 1 month. Two years prior to admission his private physician had treated him for congestive heart failure with digitalis. The patient stated that he had been stabbed with a knife in the right infraclavicular region 35 years before. Approximately 2 years after the time of injury he noted dilated veins in the area of the scar. At the same time he also became aware of a pulsating sensation in this region and felt that the circumference of his right arm became increased, as compared to the left.

On physical examination, the patient appeared to be chronically ill. The blood pressure was 108/56 mm. Hg in the right arm, and 112/50 mm. Hg in the left arm. The pulse rate was 88 per minute. The veins in his neck were distended. A large pulsating mass was noted below the right clavicle. A continuous thrill was present in this region, and the surrounding veins were noticeably dilated. The circumference of his right arm was 29 cm., whereas that of his left arm was 26 cm. at the same level. Scattered moist râles were heard over the lower part of the right lung field. The maximal cardiac impulse was in the left mid-axillary line in the sixth intercostal space. The cardiac rhythm was regular. A Grade 2 systolic murmur was heard over the base and was transmitted from the right infraclavicular region. Digital compression below the right clavicle obliterated the thrill and resulted in a slowing of the heart rate from 68 to 26 beats per minute. The edge of the liver was palpable 6 cm. below the right costal margin. There was Grade 1 pitting edema in the pretibial area.

The vital capacity was 1.2 liters. The circulation time (arm to tongue, Decholin) in the left arm was 40 seconds, and the antecubital venous pressure was 350 mm. of saline. Blood urea nitrogen was 23 mg. per 100 ml. Roentgenograms of the chest revealed massive cardiomegaly and engorgement of the pulmonary vessels. An electrocardiogram showed a normal sinus rhythm with occasional premature ventricular contractions from multiple foci. The onset of the intrinsicoid deflection was 0.06 second after the onset of ventricular depolarization in Lead V_5. The T waves were isoelectric in the limb leads and negative in Lead V_6. The data obtained at right heart catheterization on the eleventh hospital day are shown in Table I.

Because it was believed that the patient was suffering from digitalis intoxication at the time of his admission to the hospital, digitalis was withheld. Potassium chloride was prescribed, and he also received injections of mercurial diuretics. During the first 7 days of hospitalization he lost 12 pounds in weight, but became lethargic. In spite of attempts to improve his status by increasing his intake of fluid, his blood urea nitrogen rose to 60 mg. per cent on the eleventh hospital day. The initial efforts to improve his general condition with medical management were unsuccessful. The decision was made to proceed with surgical intervention, since this seemed to offer the only hope for survival. However, because the blood pressure fell to 70/60 mm. Hg on the morning on which the operation was scheduled, postponement was necessary. Therapy with norepinephrine and intravenous fluids was associated with a return to stable blood pressure at 122/70 mm. Hg. Although he responded slightly to questioning, he remained lethargic and expired the following day. Autopsy was not performed.

COMMENTS. As in Case 1, this patient also had an extremely long period between the time of his original injury and the appearance of congestive heart failure (33 years). The finding of a cardiac output below normal is of importance in the presence of a large systemic arteriovenous fistula. In this instance, systemic blood flow was severely reduced, inasmuch as a large percentage of total flow was passing through the fistula. Unfortunately, the fistula was situated beneath the clavicle, where it could only be occluded by direct manual compression. In retrospect, operation at the earliest possible moment after his admission might have been advisable. In any event, the severely reduced systemic flow indicated an unusually high operative risk.

Case 3. A 56-year-old attorney (#16-99-43) was admitted on Sept. 18, 1959, because of severe dyspnea. He had been shot accidentally in the right thigh while hunting 6 days before admission. The patient was anemic the day after injury, and was given 500 ml. of whole blood at another hospital. During the next few days he noticed dyspnea and experienced substernal discomfort. In spite of digitalis therapy his dyspnea became more severe and he was referred to this hospital for treatment.

On physical examination, the blood pressure was 130/80/70 mm. Hg. The pulse rate was 104 per minute. The left border of cardiac dullness was 12 cm. from the mid-sternal line in the fifth left intercostal space. The cardiac rhythm was regular, and the second heart sound was louder at the aortic than at the pulmonic valvular area. No murmurs were present, but a protodiastolic gallop was heard at the cardiac apex. The abdomen protruded, and the edge of the liver extended 5 cm. below the right costal margin. There was a large hematoma over

*Table I. Cardiac output determinations**

	Case 1		Case 2	Case 3	
	Preop.	*Postop.*	*Preop.*	*Preop.*	*Postop.*
Right ventricular pressure (mm. Hg)	32/22†	30/2	19‡	70/0	59/3
Oxygen consumption (ml./min.)	293	217	174	296	215
Arteriovenous oxygen difference (ml./L.)	31.1	49.1	45.1	23.7	32.3
Cardiac output (L./min.)	9.42	4.42	3.88	12.49	6.65
Cardiac index (L./min./M.^{2})	5.01	2.35	2.32	5.53	2.94

*Pressure was measured with a Statham strain-gauge pressure transducer. Gas samples were analyzed with a Beckman Model C oxygen analyzer. Analyses of blood gas were performed in duplicate by the method of D. D. Van Slyke and J. M. Neill (J. Biol. Chem. 61:523-573, 1924).

†Pulmonary artery.

‡Right atrial pressure. In this patient the catheter could not be introduced into the ventricle, so that samples of blood for analysis were obtained from the atrium.

the upper right thigh anteriorly. A continuous bruit was felt, and a continuous murmur was heard in this region. Attempts to obliterate the bruit by pressure were unsuccessful.

The antecubital venous pressure was 140 mm. of saline. Sustained pressure over the liver while the patient breathed quietly caused an increase to 260 mm. of saline. The circulation time was 18 seconds (arm to tongue, Decholin). Hemoglobin was 8.6 Gm. per cent. Roentgenograms of the chest, made at the time of admission, revealed cardiac enlargement. The right pulmonary artery was noticeably dilated near its origin. The lung fields were clear. An electrocardiogram revealed sinus tachycardia and complete right bundle branch block.

The patient was transfused with 3 units of packed red blood cells. He experienced some relief of dyspnea. On the seventh hospital day a right heart catheterization was performed (see Table I). Operation was postponed in order to permit resolution of the edema and hematoma around the site of the fistula. The patient was readmitted 8 weeks later for surgical repair of the fistula. During the interim he had lost 47 pounds in weight. At operation on Nov. 18, 1959, a fistula which measured 5 to 6 mm. in diameter was found between the superficial femoral vein and a branch of the profunda femoris artery. The fistula was divided. The patient tolerated this procedure well and recovered without incident. Five days later the right heart catheterization was repeated (see Table I).

COMMENTS. The occurrence of congestive heart failure in this patient shortly after the establishment of his arteriovenous fistula was apparently due to several causes. The presence of anemia may have increased the demands for a sustained high cardiac output. The finding of a dilated right pulmonary artery, together with right bundle branch block on the electrocardiogram and right ventricular hypertension at cardiac catheterization, indicated an abnormality of the pulmonary circulation. This undoubtedly existed prior to the time of injury. It was not associated with respiratory insufficiency of any degree and, therefore, may have represented primary pulmonary vascular disease of some type. The patient adhered strictly to his low caloric diet during the period before operation, and it was felt that this accounted for the major part of his loss of weight.

Discussion

The low resistance to the flow of blood through an arteriovenous fistula is analogous to a "short circuit" in an electrical system. The pressure in the proximal artery is the same as systemic arterial pressure but falls sharply in the fistula and in the proximal vein. The murmur and thrill result from turbulence in the region of the fistula. The maintenance of a high flow through the fistula becomes essential if the remainder of the circulatory system is to be perfused. This bizarre pattern of flow regularly affects the vessels in the region of the fistula. The proximal artery becomes enlarged and tortuous. True aneurysmal dilatation is not uncommon and occurred in the present Case 1. The veins in the region of the fistula exhibit thickened walls, with muscular hypertrophy and intimal sclerosis. Burton[1] has pointed out that tension in the vascular wall is directly proportional to the radius of the vessel. Inasmuch as the regional artery is regularly enlarged, one wonders whether systemic arteriovenous fistulas, once established, do not gradually increase in size.

Frank and co-workers[2] found that experimental fistulas with a flow of less than 20 per cent of the control cardiac output did not compromise systemic flow; that is, cardiac output increased sufficiently to compensate for the flow through the fistula. In the case of large fistulas the cardiac output did not increase sufficiently, and flow to

the systemic vessels was decreased. The increased cardiac output in patients with peripheral arteriovenous fistulas has been well documented. A large number of patients have been studied by means of ballistocardiography,[3] dye dilution measurements,[4] and measurements by the direct Fick principle.[5] The cardiac output correlates directly with the size of the fistula: the larger the communication the greater the cardiac output. Temporary or permanent occlusion of the fistula causes an abrupt decrease in the cardiac output.

The alterations in hemodynamics secondary to an open peripheral arteriovenous fistula can be summarized as adjustments to the low-resistance channel provided by the fistula. The characteristic increase in cardiac output constitutes a compensatory mechanism which attempts to maintain an adequate peripheral arterial pressure.

Surprisingly few measurements of cardiac output have been reported during periods of congestive heart failure in patients with peripheral ateriovenous fistulas. Muenster, Graettinger and Campbell[5] studied the cardiac output in 6 patients with arteriovenous fistulas. Two of these patients had severe congestive heart failure at the time of study. Cardiac output was greater than normal in both instances and decreased significantly with exercise. It was interesting that the effect which compression of the fistulas had on cardiac output agreed closely with the results obtained after surgical repair in their series. The patients in the present study had unequivocal signs of congestive heart failure, including cardiomegaly, hepatomegaly, peripheral edema, and increased venous tone. The long time interval between the establishment of an arteriovenous fistula and the appearance of congestive heart failure suggests that, in a majority of instances, the heart can adjust very well to the work load imposed by the increased cardiac output.[6] The present Case 2 is of interest because the patient's cardiac output was apparently the lowest recorded in anyone with this disease.

The question arises whether the late appearance of congestive heart failure in some of these patients is due to (a) an increased size of the fistula, (b) a decreased cardiac reserve, or (c) other conditions which affect myocardial function. Although proof is lacking, it seems reasonable to conclude that in certain patients each of these factors may be important. Whatever the natural course of the disease, the physician's responsibility is clear: to obtain prompt and adequate surgical treatment.

Summary

1. Three patients with arteriovenous fistulas in whom cardiac output was determined during a period of congestive heart failure were reported upon. The cardiac output was greater than normal during heart failure in two of the patients and less than normal in the other patient studied 7 days prior to death.

2. After the fistulas had been repaired, and the patients had recovered from congestive heart failure, the cardiac output was found to be decreased. Certain hemodynamic considerations were discussed.

Dr. M. Hara, Professor of Surgery, performed the operations on the patients of Cases 1 and 3. The authors are grateful for his permission to publish these cases.

REFERENCES

1. Burton, A. C.: Peripheral circulation. Notes, Medical Basic Science Course, Army Medical Service Graduate School **2**:727, 1950-1953.
2. Frank, C. W., Wang, H. H., Lammerant, J., Miller, R., and Wégria, R.: An experimental study of the immediate hemodynamic adjustments to acute ateriovenous fistulas of various sizes, J. Clin. Invest. **34**:722, 1955.
3. Warren, J. V., Nickerson, J. L., and Elkin, D. C.: The cardiac output in patients with arteriovenous fistulas, J. Clin. Invest. **30**:210, 1951.
4. Schreiner, G. E., Freinkel, N., Athens, J. W., and Stone, W., III.: Cardiac output, central volume and dye injection curves in traumatic arteriovenous fistulas in man, Circulation **7**:718, 1953.
5. Muenster, J. J., Graettinger, J. S., and Campbell, J. A.: Correlation of clinical and hemodynamic findings in patients with systemic arteriovenous fistulas, Circulation **20**:1079, 1959.
6. Dorney, E. R.: Peripheral A-V fistula of fifty-seven years' duration with refractory heart failure, Am. Heart J. **54**:778, 1957

"Auricularization" of right ventricular pressure curve

*Sergio Dalla-Volta, M.D.**
*Gino Battaglia, M.D.***
*Ennio Zerbini, M.D.***
Padova, Italy

Recording of uncommon pulse contours from the right ventricle in different endocardial or myocardial diseases has been reported with increased frequency in recent years because of the widespread use of cardiac catheterization for hemodynamic studies in patients who are considered not suitable for cardiac operations.

In most cases the abnormalities observed in the right ventricular pulse contour are consistent with the so-called adiastolic syndrome, and are characterized by a protodiastolic dip and a telediastolic plateau. The right auricular pressure curve generally exhibits an M-shaped aspect, which may also be present in the left auricular pressure curve if the left sections of the heart are involved, too.

The patterns show some analogies with the pulse contour recorded in constrictive pericarditis, although as has been pointed out recently, the hemodynamics present some distinctive features.[6]

Also recently, Bayer and associates[2] obtained an auricular pressure tracing from the right ventricle and the pulmonary artery in a case of possible endocardial fibroelastosis, and such a tracing has been recorded occasionally in the inflow tract of the right ventricle, in the so-called atrioventricular common chamber in Ebstein's disease.[4,11]

We had occasion to observe, recently, two proved cases of endocardial or myocardial fibrosis in which cardiac catheterization showed an auricular tracing in the right ventricle and in the pulmonary artery. Whereas in the first patient the final diagnosis was of "primitive endocardial fibrosis," in the second subject the fibrosis of the right ventricle was dependent on an extensive myocardial infarction which produced a complete involvement of the right ventricle.

Case reports

Case 1. L. A., a 26-year-old woman, entered our Department on Nov. 2, 1956, complaining of mild exertional dyspnea which had been present for 2 years. She had had no complaints previous to these symptoms, and no cardiological examination had been made before the time of this admission.

Physical examination revealed the patient to be in good condition: the blood pressure was 120 70 mm. Hg, and the pulse rate was 90 per minute. There was a 2-plus jugular engorgement. The thorax appeared to be normal. The heart was clinically enlarged, and a mid-diastolic gallop rhythm was noted, but there were no murmurs. The liver was moderately enlarged, tender, and painless; the spleen was slightly enlarged. No other abnormalities were detected on clinical examination.

Chest x-ray films showed a moderate enlargement

From the Cardiovascular Unit, Department of Internal Medicine, University of Padova Medical School, Padova, Italy.
Received for publication June 20, 1960.
*Chief, Cardiopulmonary Laboratory.
**Assistant, Cardiovascular Unit.

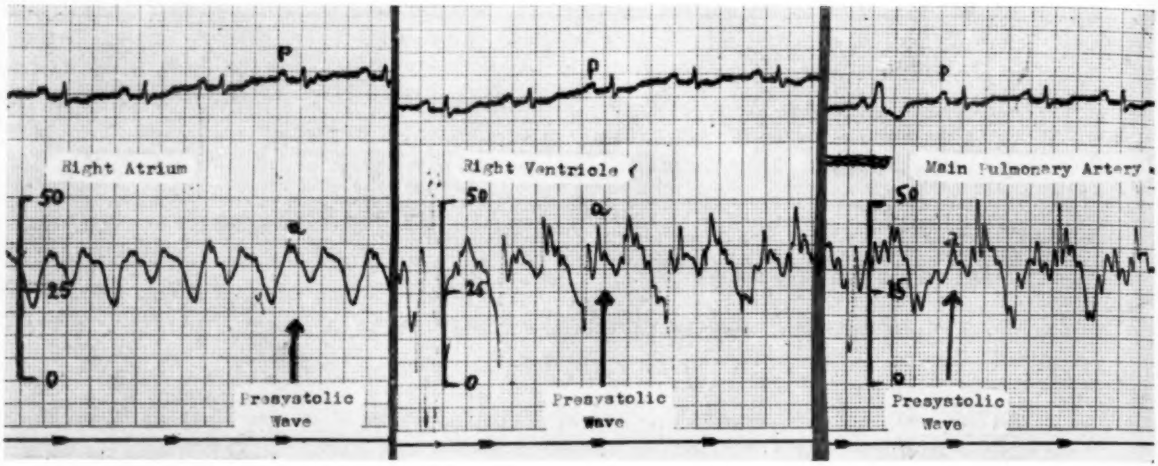

Fig. *1.* Case 1. Pressure curve from the right atrium, right ventricle, and main pulmonary artery in a case of fibroelastosis, showing a presystolic wave (*a*) in the right ventricle and main pulmonary artery.

of the cardiac shadow, especially of the right atrium and right ventricle. There was a slight dilatation of the pulmonary artery, but no signs of pulmonary congestion.

An electrocardiogram revealed a sinus rhythm, no alterations in conduction, a vertical electrical position, and signs of right atrial and ventricular hypertrophy.

The laboratory studies showed: blood urea nitrogen, 0.20 Gm. per cent; fasting blood glucose, 1.05 Gm. per cent; Wassermann reaction, negative; sedimentation rate, Katz 15; erythrocyte count, 4,200,000 and hemoglobin 12.5 Gm. per cent; leukocyte count, 7,500, with 20 per cent lymphocytes, 5 per cent monocytes, 75 per cent neutrophils; antistreptolysin-O titer, 166 units per cubic centimeter. The urinalysis was normal.

Cardiac catheterization (Table I), performed on November 12, demonstrated a severe hypertension in both venae cavae and in the right auricle. In the right ventricle and pulmonary artery the systolic pressure was only slightly elevated, whereas the right ventricular diastolic pressure was clearly elevated. Pulmonary wedged pressure was markedly increased. The cardiac output was decreased; the pulmonary resistances were normal. Analysis of the pulse contour (Fig. 1) showed an "M" appearance in the right atrium. In the right ventricle, two tops were observed: the first coincided with the presystolic wave of the right auricular tracing, and the second was related to the ventricular contraction and was followed by a protodiastolic dip with a late diastolic plateau. In the main pulmonary artery the presystolic wave was again noted, whereas the pulse tracing recorded from the right and left pulmonary branches was normal. The pulmonary wedged pressure tracing did not show abnormalities.

The possibility of either an anomaly of the tricuspid valve or constrictive pericarditis was considered to be consistent with the hemodynamic data, but, because the patient refused further investigations, she was discharged on November 25.

After she was discharged, the exertional dyspnea increased and mild ankle edema was noted. In March, 1957, the patient entered a hospital outside of Italy. Cardiac catheterization was repeated, but pertinent data are not available; however, a diagnosis of constrictive pericarditis was made, and the patient underwent a cardiac operation. During the thoracotomy, no signs of pericardial involvement were observed. Because of the appearance of the heart, possible myocardial disease was suspected and right auricular biopsy was performed. This showed an endocardial fibroelastosis. The final diagnosis was "primitive endocardial fibrosis." The recovery was uneventful and the patient was discharged 1 month later. The successive course of the disease remained unchanged, and 3 years later (February, 1960) the patient was in rather poor condition.

Case 2. T. N., a 21-year-old man, had been symptomless and active in his work as a bricklayer until Feb. 18, 1957, when he underwent an operation for acute appendicitis. Five days later, on February 23, the patient experienced a sudden aching pain in the precordium and left shoulder, which radiated to the left arm; he was without fever or dyspnea. The blood pressure fell from 125/75 to 90/60 mm. Hg. An electrocardiogram (Fig. 2), taken on the same day, showed a sinus rhythm, a normal P wave, a tall R wave in Leads D_2, D_3, and aV_F, a deep S wave in Lead V_2, and an elevated R wave in Lead V_5; a monophasic current of injury was present from Lead V_1 to Lead V_4. During the following days, while the monophasic wave gradually disappeared, anterior ischemia and signs of diaphragmatic necrosis (deep Q wave in Leads D_2, D_3, and aV_F, and marked diminution of R voltage in the same leads) were noted (Fig. 3).

The diagnosis of postoperative myocardial infarction was made, and the patient was treated with bed rest, anticoagulants, and strophantin. His condition gradually improved, and the electrocardiographic evolution was typical, but at the same time a progressively increasing tall P wave was observed in Leads D_2 and D_3 and the precordial leads. After this event of myocardial infarction the patient began to complain of exertional dyspnea

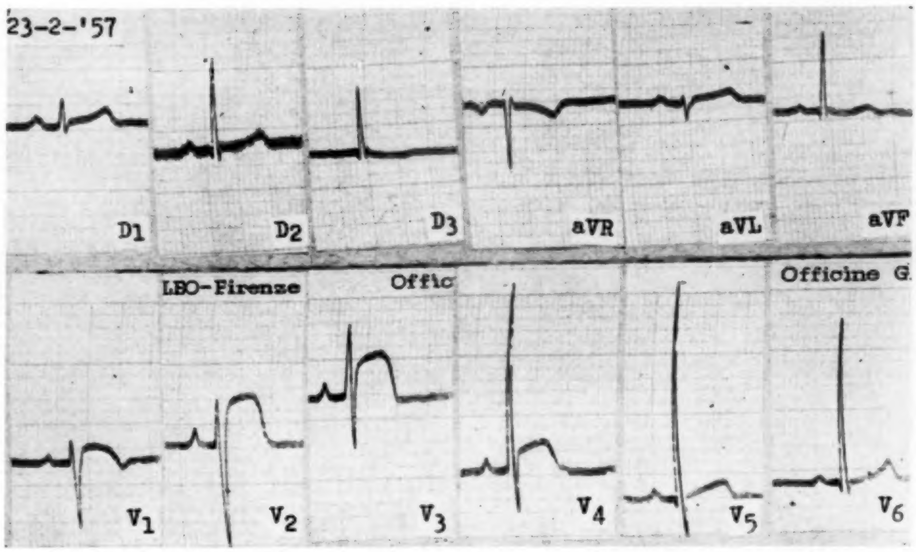

Fig. 2. Case 2. Electrocardiogram (3 hours after the appearance of precordial pain): monophasic current of injury from Lead V_1 to Lead V_4.

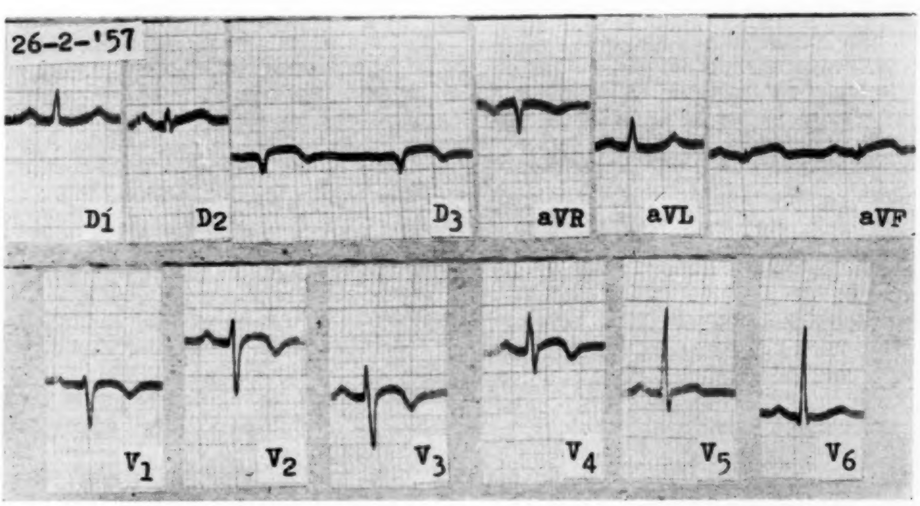

Fig. 3. Case 2. Electrocardiogram (3 days after the appearance of precordial pain): signs of diaphragmatic necrosis.

and fatigue. Because of these disturbances the patient was admitted to our Department on Sept. 6, 1957.

At the time of admission, physical examination showed him to be a well-nourished man. The blood pressure was 125/90 mm. Hg, and the pulse rate was 100 per minute. The heart was clinically enlarged; the first heart sound was normal and not split, and the second pulmonary sound was reinforced (Fig. 5). The liver was felt 2 fingerbreadths below the costal margin, was tender and painless. No other physical abnormalities were detected. The erythrocyte count was 5,080,000 and hemoglobin was 16 Gm. per cent; leukocyte count, 6,500, with 33 per cent lymphocytes, 2 per cent monocytes, and 65 per cent neutrophils. The urinalysis was negative. Blood urea nitrogen was 0.25 Gm. per cent; blood glucose was 0.84 Gm. per cent; sedimentation rate was normal; the Wassermann reaction was negative; the antistreptolysin-O titer was 166 units per cubic centimeter. The other laboratory findings were normal.

A chest film showed an enlarged heart; enlargement was due mainly to dilatation of the right ventricle. The pulmonary arch was concave. The electrocardiogram (Fig. 4) showed sinus rhythm, a tall P wave, and a P mean axis of about +60. The QRS axis was −100. There were deep Q waves in Leads D_2, D_3, and aV_F, and an rS complex of small amplitude from Lead V_1 to Lead V_6. No definitive changes of the RS-T segment were present, but the T wave was flattened in Leads D_1 and aV_L

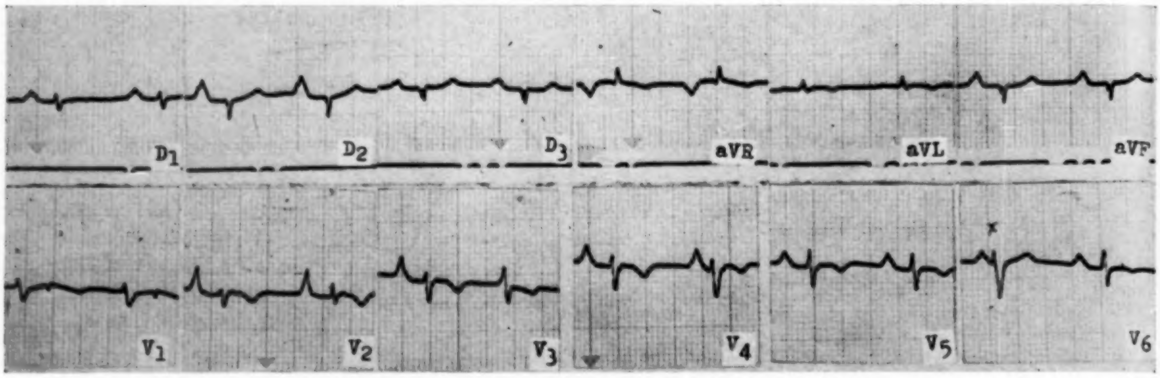

Fig. *4*. Case 2. Seven months after the appearance of a diaphragmatic necrosis, a right auricular hypertrophy is noted (tall P wave in Leads D_2, D_3, and aV_F).

and inverted, symmetrical, and negative in the precordial leads.

Because the clinical and electrocardiographic data were considered to suggest a pulmonary impairment associated with the past diaphragmatic myocardial infarction, catheterization of the heart was planned. On November 30, the patient was catheterized, without complication, and the pertinent data are summarized in Table I. There was a mild rise of pressure in the right ventricle and pulmonary artery, whereas the right auricular pressure was markedly enhanced and the pulmonary

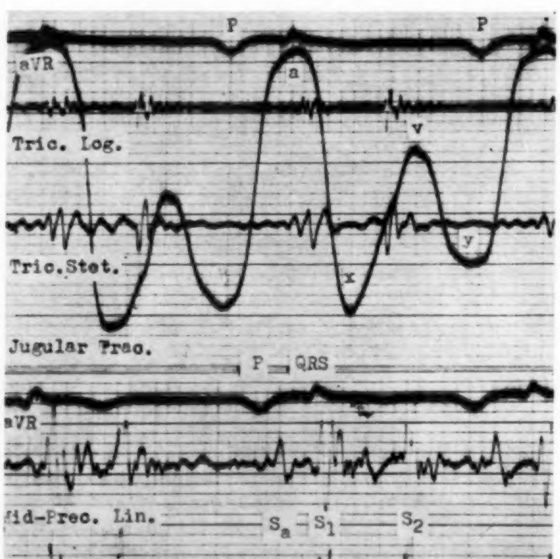

Fig. *5*. Case 2. Phonocardiogram in the mid-precordium, showing a loud atrial sound (S_a) and a first sound (S_1), single, not duplicated. In the tricuspid area the first sound is also single and of low frequency and intensity. In the jugular tracing a giant *a* wave is noted.

wedged pressure was normal. In the right atrium a giant "a" wave was present and was transmitted to the right ventricle and main pulmonary artery, but not to the right and left branches; in the right ventricle the normal systolic wave was scarcely visible, and in the pulmonary artery the dicrotic notch was not observed (Fig. 6).

The intracavitary electrocardiogram (Fig. 7) showed: (a) in the main pulmonary artery a giant, negative P wave; (b) in the right ventricle a positive, tall P wave, and an rS complex of low amplitude, with a normal, negative T wave; (c) in the lower right atrium a giant, positive P wave, and in the mid-upper right atrium a giant, negative P wave. Therefore, the intracavitary electrocardiogram confirmed the existence of right atrial hypertrophy.

A possible diagnosis of "unknown" myocardial disease or cardiac tumor was considered to be consistent with the hemodynamic data, and the patient was discharged on Feb. 15, 1958. He was followed up in the outpatient unit of our Department, and for more than 15 months his general condition was unmodified.

On June 26, 1959, the patient was readmitted, complaining of very severe exertional dyspnea, which had been present for 3 days. His general condition was not changed, but the cardiac shadow showed a further augmentation. The blood pressure was 100/75 mm. Hg, and the pulse rate was 110 per minute. The electrocardiogram was unaltered, and laboratory tests were normal.

In order to establish the possibility of an operation by means of cardiac bypass, catheterization of the right heart was repeated (Fig. 8). In comparison with previous hemodynamic findings, the height of the "a" wave was diminished in the right auricle, right ventricle, and main pulmonary artery; the systolic wave had almost completely disappeared from the right ventricle and pulmonary artery, so that it was impossible to recognize the different cavities and vessels of the right heart from the pulse contour. Moreover, there was equalization of pressure in the right auricle and ventricle, and in the pulmonary artery.

A diagnosis of intracardiac fibroelastosis was suggested, and the patient was discharged, being considered not suitable for open-heart operation.

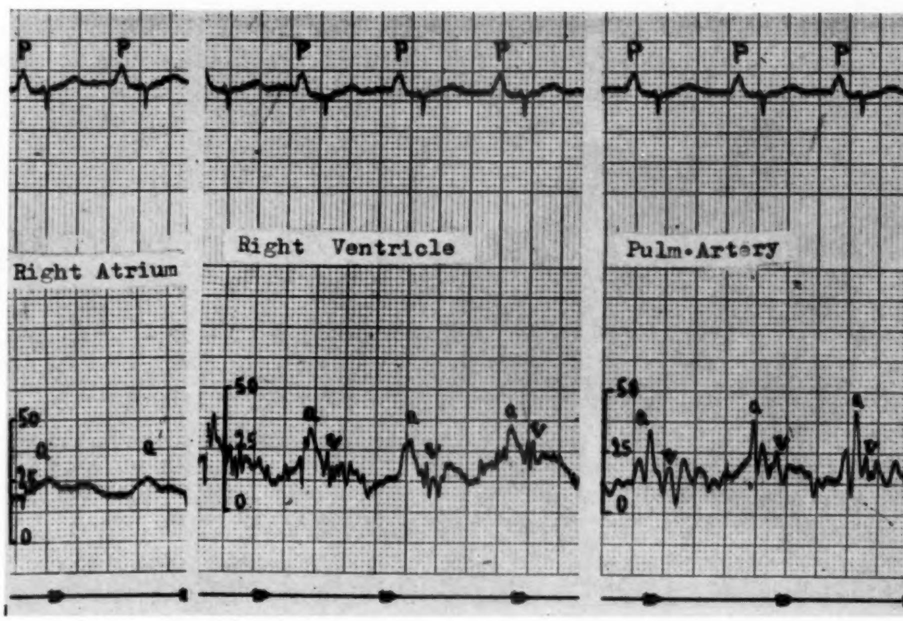

Fig. *6*. Case 2. Pressure curve from the right atrium, right ventricle, and main pulmonary artery in a case of infarction of the right ventricle. Note the presence of an elevated presystolic wave (*a*) in the right ventricle and main pulmonary artery.

On September 27, he was admitted in an extremely severe condition, with very accentuated orthopnea, cyanosis, and somnolence. Despite all therapy the patient died the following day.

AUTOPSY. Only the abnormalities pertinent to the heart will be reported in detail. There was an engorgement of liver, spleen, and kidneys: both lungs were ischemic; no other major abnormalities were noted. The heart weighed 300 grams. The right ventricle was extremely dilated, and its wall measured only 2 mm. across. The papillary muscles were thin, white in color, and almost completely transformed into fibrous tissue. The right auricle was distended and greatly hypertrophied. The left atrium and left ventricle were normal. The pulmonary artery was normal, but the aorta was hypoplastic. Both coronary arteries arose from the aorta: the left coronary artery was normal, without signs of atheroma or sclerosis; the right coronary artery was greatly hypoplastic, but without obstructions.

The microscopic appearance confirmed the replacement of the muscular tissue of the right ventricle with fibrotic tissue, in which the muscle cells and vessels were practically absent. In the left ventricle, no major microscopic abnormalities were detected, except some small sclerotic areas.

The final pathologic diagnosis was: sclerosis of the right ventricle after a myocardial infarction without coronary obstruction.

Discussion

In spite of some features in common in the intracardiac pulse contour, these patients have presented a different clinical course and different pathologic lesions. The first patient had apparently a rather mild form of endocardial disease which involved the right auricle and the right ventricle, but probably not the left heart. This was demonstrated by the biopsy of the right auricular appendage and by the

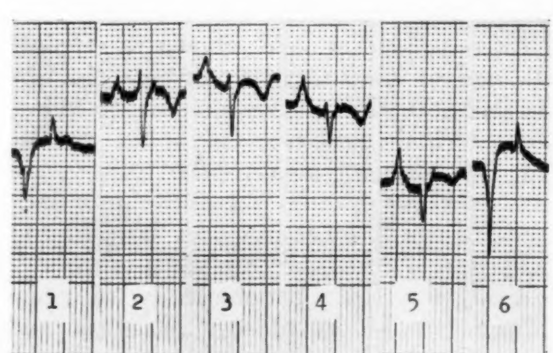

Fig. 7. Case 2. Intracavitary ECG obtained from: *1*, main pulmonary artery; *2*, outflow tract of the right ventricle; *3*, mid-apex right ventricle; *4*, right ventricle below tricuspid valve; *5*, lower right atrium; *6*, upper right atrium.

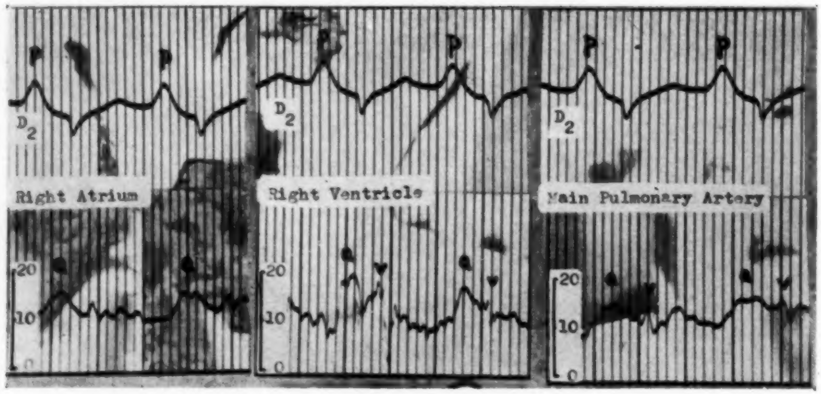

Fig *8*. Case 2. Pressure curve from the right atrium, right ventricle, and main pulmonary artery recorded 3 months prior to the death of the patient. Note the presence of a prominent presystolic wave (*a*) in the right ventricle and main pulmonary artery, with equalization of pressure in all the cavities.

presence of a clearly visible "a" wave in the right ventricle and in the main pulmonary artery, while the pulmonary wedged pressure was normal and no transmission of auricular waves to the brachial artery was present. Three years after the second hemodynamic study and the surgical exploration of the heart, no definite changes had occurred, and the patient presented a chronic disease with recurrent episodes of right heart failure, rather well controlled by digitalis and diuretics.

In the second patient the disease began abruptly and ended 2½ years later with death from complete heart failure. The electrocardiogram had shown a typical picture of diaphragmatic myocardial infarction, in which it was possible to follow the normal electrocardiographic course: the recording of a current of injury, together with the rapid diminution of amplitude of the R wave in Leads D_2, D_3, and aV_F, and successively the appearance of a deep Q wave in the same leads, with disappearance of the monophasic wave and appearance of posterior ischemia. Later, while the signs of myocardial infarction persisted until the end, a pulmonary P wave developed, suggesting a chronic disease of the pulmonary artery and possible pulmonary hypertension. Actually, the first and second catheterization studies of the heart revealed the disappearance of an effective right ventricular contraction (the normal ventricular ejection wave had disappeared) and the maintenance of the pulmonary circulation by means of a strong auricular contraction (as evidenced by the recording of a giant "a" wave in the right ventricle and in the main pulmonary artery). The importance of right atrial contraction in supporting the pulmonary blood flow is also stressed by the coincidence of right heart failure with impairment of right auricular contractility. In effect, the second hemodynamic study, performed when the signs of right heart failure were present, revealed a decline of the presystolic wave, together with the reduction of cardiac output.

The pathologic examination showed an extensive replacement of muscular tissue by fibrotic tissue in the right ventricle, whereas the right auricular muscle was greatly hypertrophied, and the left heart cavities did not show signs of impairment. No coronary occlusion was detected, but there was a marked hypoplasia of the right coronary artery; this finding, together with the signs of myocardial infarction, supports the possibility of an acute myocardial infarction not dependent on a coronary occlusion, but probably related to the fall of blood pressure due to the shock of operation. The acute postoperative hypotension in the presence of a congenitally underdeveloped right coronary artery may have precipitated an acute coronary insufficiency, due to functional vasospastic mechanism. The possibility of cardiac infarction in the absence of coronary obstruction, as a consequence of a sudden fall of blood pressure, is well known.[5,8,9] Since the original paper of

Friedberg and Horn,[9] myocardial infarctions in the absence of coronary occlusion have been found rarely (only 0.7 per cent in the gross anatomic material of Goder[10]). This points out the importance of an isolated sudden fall of blood pressure as the cause of coronary insufficiency.

Infarction of the right ventricle is exceedingly rare.[3,14] Moreover, it does not present distinctive electrocardiographic patterns,[7,15] and is followed without exception by death in the first few days, depending on the contemporary involvement of the left ventricle due to the lack of a particular distribution of coronary blood flow for each ventricle.[13] To our knowledge, no cases of isolated right ventricular infarction in human beings have been reported; in the experimental field, however, the production of right ventricular massive infarction is not usually followed by death,[12] and some authors[1,12] affirm that the right ventricle is not essential in the performance of cardiac function, at least for a few months.

In our case the electrocardiographic signs of right ventricular infarction were evident and were dependent on the fact that the inferior and anterior surfaces of the heart were formed by the right ventricle; the replacement of muscular tissue by connective tissue was not followed by immediate death, since the right auricle did maintain the pulmonary circulation. Possibly there was a congenital hypofunction of the right ventricle, so that the complete loss of its contractility was not so severe as would have been that of a well-functioning right ventricle. However, the late appearance of signs of right atrial hypertrophy demonstrates that the right auricle had supplied the declining function of the right ventricle only after acute coronary insufficiency had developed.

As previously mentioned, recording of auricular waves from the right ventricle has been observed by some authors. This has been noted occasionally in Ebstein's disease in the so-called atrioventricular common chamber (so-called "ventricularization" of right auricular pulse contour).

More recently, Bayer and co-workers[2] noted a similar pattern in the right ventricular chamber and in the pulmonary artery in a case of supposed endocardial fibroelastosis. These German authors suggest the possibility that the right atrium participates actively in the dynamics of the heart as a "second ventricle," and this would be demonstrated also by the equalization of pressure in all cavities.

A giant "a" wave in the right atrium as well as the equalization of the mean pressure can be recorded in cases of con-

Table I. *Catheterization findings*

	A.L., 26-year-old woman (Cath. No. 427)		*T.N., 30-year-old man (Cath. No. 541)*		*T.N., 30-year-old man (Cath. No. 907)*	
	Intracardiac pressures (mm. Hg)	*Oxygen content (vol. %)*	*Intracardiac pressures (mm. Hg)*	*Oxygen content (vol. %)*	*Intracardiac pressures (mm. Hg)*	*Oxygen content (vol. %)*
R.A.	35 19 25	10.78	25 17 20	12.90	18 11 14	—
R.V.	42 15 —	10.76	30 10 —	12.95	20 9 —	—
P.A.	42 16 26	10.81	30 10 18	13.07	18 11 15	14.67
P.W.P.	— — 17	—	— — 13	—	— — 10	—
B.A.	125 85 —	16.75	120 75 —	18.50	135 80 —	21.89
O_2 capacity	18.74 vol. %		20.24 vol. %		24.75 vol. %	
O_2 saturation	89 %		91 %		88 %	
O_2 consumption	160 c.c./min.		190 c.c./min.		185 c.c./min.	
Cardiac output	2.7 L./min.		3.5 L./min.		2.6 L./min.	
Cardiac index	1.6 L./min./M.^{2}		1.9 L./min./M.^{2}		1.4 L./min./M.^{2}	
P.T.R.	770 dynes/sec./cm.$^{-5}$		395 dynes/sec./cm.$^{-5}$		480 dynes/sec./cm.$^{-5}$	
P.A.R.	266 dynes/sec./cm.$^{-5}$		110 dynes/sec./cm.$^{-5}$		160 dynes/sec./cm.$^{-5}$	

strictive pericarditis or in other adiastolic states.[8] However, in not one of the aforementioned disease states has a presystolic wave been observed outside the right auricle.

In our cases, an auricularization of the right ventricular pulse was present, yet its significance is different in the two cases. In the first patient the presystolic wave was followed by a normal systolic wave which was also recorded in the pulmonary artery, thus demonstrating that the right ventricle had partially maintained its propelling force and contributed to the pulmonary circulation. In the second patient, the first catheterization showed a very tall presystolic wave in the right ventricle, and only some small deflections in coincidence with the ventricular contraction. The pulmonary valves were opened only by the atrial contraction. When the patient was recatheterized, 3 months prior to his death, the efficiency of the right ventricle was found to be further reduced, since the atrial systolic wave was diminished in amplitude, the systolic remnants of ventricular contraction were no longer visible, and the cardiac output was greatly decreased. This clearly demonstrates that the right atrium alone maintained the pulmonary output.

It is interesting to observe that the presystolic wave was more elevated in the right ventricle and in the main pulmonary artery than in the right atrium. This was due possibly to the loss of elastic properties of the right ventricle, so that the ventricular wall, which was inextensible, behaved as a stiff pipe. The loss of the normal distensibility of the right ventricle produced, when the blood entered the cavity, a diminished recoil of the ventricular wall, which was responsible for the augmented intraventricular pressure. The disappearance of the "a" wave in the left and right branches of the pulmonary artery can be explained on the basis of the maintenance of pulmonary recoil.

Previous cases, as well as our patient, suggest the possibility that different pathologic and clinical entities can occasionally give similar hemodynamic pictures. Right auricular waves from the right ventricular chamber and the main pulmonary artery can be recorded in instances of complete right ventricular disability, which may or may not be compatible with life. The possibility of a prolonged survival depends mostly on the pumping capacity of the right auricle, and its failure has the significance of irreversible right heart failure.

Summary

Two cases are presented which show particular hemodynamic patterns, characterized by the recording of an auricular pressure curve from the right ventricle and the main pulmonary artery.

Anatomic study proved the clear distinction between the two subjects. In the first patient, the biopsy of the right auricular appendage, performed during the cardiac operation, showed a diffuse endocardial fibroelastosis; in the second patient, at autopsy a massive fibrosis of the right ventricle, dependent upon an infarction of the right ventricle, was observed.

Evidence is presented to support the view that the pulmonary blood flow was maintained by the contraction of the right atrium, which was greatly hypertrophied, whereas the right ventricle acted merely as a passive stiff chamber.

The right heart insufficiency appeared when the right atrium failed to support the pulmonary circulation; the congestive failure coincided with the failure of the right atrium.

From the study of these cases, the nonessentiality of the right ventricle in the pump mechanism of the heart previously observed in the experimental field seems to be demonstrated also in human beings.

REFERENCES

1. Bakos, A. C. P.: The question of the function of the right ventricular myocardium; an experimental study, Circulation **1**:724, 1950.
2. Bayer, O., Brix, J., and Meyer, R. D.: Zur Fibroelastosis endocardica unter besonder Berucksichtigung der Diagnose intra vitam, Arch. Kreislaufforsch. **28**:217, 1958.
3. Bean, W. B.: Infarction of the heart: clinical course and morphological findings, Ann. Int. Med. **12**:71, 1938.
4. Broadbent, J. C., Wood, E. H., Burchell, H. B., and Parker, R. L.: Ebstein's malformation of the tricuspid valve: report of 3 cases, Proc. Staff Meet Mayo Clin. **28**:79, 1953.
5. Condorelli, L.: L'infarto emorragico prestatico del cuore, Comun. Soc. Med. Chir., Catania, **10**:13, 1942.

6. Dalla-Volta, S., Battaglia, G., and Zerbini, E.: Diagnosi differenziale emodinamica delle adiastolie, Mal. cardiovasc. **1**:2/63, 1960.
7. Dressler, W., and Roesler, H.: Variations in the deviation of S-T in anterior wall infarction, AM. HEART J. **35**:58, 1948.
8. Farulla, A., Sangiorgi, M., and Bompiani, G. D.: Condorelli's prestatic infarction, Cardiologia **33**:269, 1958.
9. Friedberg, C. K., and Horn, H.: Acute myocardial infarction not due to coronary occlusion, J.A.M.A. **112**:1675, 1939.
10. Goder, G.: Der akute tödliche Myokardinfarkt, Ztschr. Kreislaufforsch. **49**:105, 1960.
11. Van Lingen, B., McGregor, M., Kaye, J., Meyer, M. J., Jacobs, H. B., Braudo, J. L., Bothwell, T. H., and Elliot, G. A.: Clinical and cardiac catheterization findings compatible with Ebstein's anomaly of the tricuspid valve. A report of two cases, AM. HEART J. **43**:77, 1952.
12. Starr, I., Jeffers, W. H., and Meade, R. H.: The absence of conspicuous increments of venous pressure after severe damage to the right ventricle of the dog, with a discussion of the relation between clinical congestive failure and heart disease, AM. HEART J. **26**:291, 1943.
13. Wade, W. G.: The pathogenesis of infarction of the right ventricle, Brit. Heart J. **21**:545, 1959.
14. Wartman, W. B., and Hellerstein, H. K.: The incidence of heart disease in two thousand consecutive autopsies, Ann. Int. Med. **28**:41, 1948.
15. Wolferth, C. C., Bellet, S., Livesey, M. M., and Murphy, F. D.: Negative displacement of the S-T segment in the electrocardiogram and its relationship to positive displacement; an experimental study, AM. HEART J. **29**:220, 1945.

Correlation of clinical information in the standard 12-lead ECG and in a corrected orthogonal 3-lead ECG

Hubert V. Pipberger, M.D.
Stanley M. Bialek, M.D.
Joseph K. Perloff, M.D.
Harold W. Schnaper, M.D.
Washington, D. C.

The extent to which 3 orthogonal electrocardiographic leads record all electrical information which is available from the body surface has been debated since the advent of vectorcardiography. Can the standard 12-lead electrocardiogram be replaced by 3 orthogonal leads without appreciable loss of clinical information? Problems related to such reduction in number of leads have been amply discussed previously.[1] Recent attempts to automate ECG analysis by use of electronic computers have emphasized the necessity of a reduction of data and elimination of redundant information.[2,3] Reduction in the number of leads has become, therefore, a prime objective of electrocardiographic research. Before such a step can be recommended, however, conclusive evidence is required that no information of clinical significance is sacrificed by the use of fewer leads.

It has been suggested that recording preferentially from local portions of the heart by use of precordial leads may provide information not supplied by an orthogonal 3-lead system.[4-7] On the other hand, some proponents of orthogonal lead systems believe that practically all electrical information available from the body surface could be attributed to a single, *fixed*, point-like dipole equivalent.[8-10] This hypothesis has been questioned,[11-16] however, and no generally accepted concept on the physical characteristics of the heart as a generator of current exists at present.

Recent studies by Scher and associates[17] shed further light on the question of the minimum number of required leads. Using electronic computers, they investigated mathematically how many independent variables or "factors" (in linear combination) can account for a variety of surface leads. The number of independent variables equals the number of leads required. This study indicated that 3 leads were sufficient to record all electrical information from the body surface of normal subjects. The authors pointed out that the assumption of a dipole equivalent is not a necessary condition for the reduction of leads to 3.

Other approaches to the problem of determining whether 3 leads are adequate have consisted mainly in qualitative comparisons between vector loops and standard ECG leads.[18,19] Generally, good agreement between the two types of data has been

From the Veterans Administration Hospital, Mt. Alto, and the Cardiovascular Research Laboratory, Department of Medicine, Georgetown University School of Medicine, Washington, D. C.
Supported in part by a grant from the American Heart Association.
Presented at the Third Annual Meeting of the Biophysical Society, Feb. 25-27, 1959, Pittsburgh, Pa.
Received for publication May 18, 1960.

found, and the orthogonal leads were considered to be sufficient for a complete description of the body surface ECG. However, the number of cases studied in this fashion has been relatively small.

A detailed comparison of the clinical information contained in the 12-lead ECG and 3 orthogonal scalar leads (Frank's system[20]) has been reported recently by Abildskov and associates[21] in a series of 71 cases. A search for diagnostically significant patterns found in the standard leads was made in orthogonal 3-lead records. In almost 10 per cent of the cases, such diagnostic features could not be recovered in the orthogonal leads. Patterns of leads from 3 directions were compared, however, with those from 12 directions. This discrepancy in the display of data obviously favors the standard leads by a ratio of 1:4. Information may have been contained in the 3 orthogonal leads but was not displayed in the familiar patterns of the standard ECG which were used as the only criteria for the comparison.

In order to circumvent such shortcomings, a more refined approach to the same problem was used in the present study. A first comparison was made between the standard 12-lead ECG and 3 corrected orthogonal leads (Schmitt's SVEC-III system[22]). Additionally, in order to obtain a display of data in the orthogonal ECG which is comparable to that in the standard ECG, a second correlation was made. The 3 basic orthogonal components were resolved[23] to obtain additional leads from directions generally assumed for the standard ECG. Resolved leads merely represent linear combinations of the 3 basic leads. Therefore, they cannot possess any new information not contained in the basic components. In this fashion, however, a directly comparable display of data is obtained for both types of leads. The readings of the two sets of records were performed by independent interpreters in order to avoid any bias through knowledge of findings in a record to be compared. This blind feature of the study was an essential safeguard because it is common experience that one may read information into an electrocardiogram.

Correlations of the content of clinical information do not lead to a physical definition of the heart as a generator of current and are purely qualitative. The advantage of a clinical correlation, however, lies in its immediate applicability, without the need for theoretical notions on the heart as a generator of current.

Materials and methods

A random selection of 261 patients who showed abnormal features in their electrocardiograms was used for the present study. The distribution of their ECG diagnoses is shown in Table I. In each of these cases a standard 12-lead electrocardiogram was taken together with a corrected orthogonal 3-lead electrocardiogram (Schmitt's SVEC-III system[22]), including resolved leads from directions comparable to those of the standard leads. The design of the switching type of resolver used was described previously.[23] An example for the method of arriving at resolved leads is shown in Fig. 1. The directions of the resolved leads are indicated in Fig. 2. They were designated according to their plane of projection. Resolved leads in the frontal plane which corresponded to the standard limb leads were called XY leads, in the horizontal plane, XZ leads, and in the sagittal plane, YZ leads. An angular scale with clockwise rotation from 0 to 360° was used for each plane; 0° was always to the right of the observer (Fig. 2). Two leads in the horizontal plane (XZ 120 and 150) and 4 leads in the sagittal plane (YZ 30, 60, 300, and 330) have no counterpart in the standard ECG. Except in two cases, indicated below, they were not used for the correlation. A 4-channel direct-

Table I. *Distribution of electrocardiographic interpretations**

Left ventricular conduction defect	15
Right ventricular conduction defect	19
Intraventricular conduction defect, type undetermined	1
Right ventricular hypertrophy	9
Left ventricular hypertrophy	89
Biventricular hypertrophy	8
Myocardial infarction	
1. Anterior and anteroseptal	37
2. Diaphragmatic and high posterior	42
3. Lateral	15
Nonspecific changes	50
	285

*In 24 out of 261 cases, more than one ECG diagnosis was made. These have been included in this tabulation.

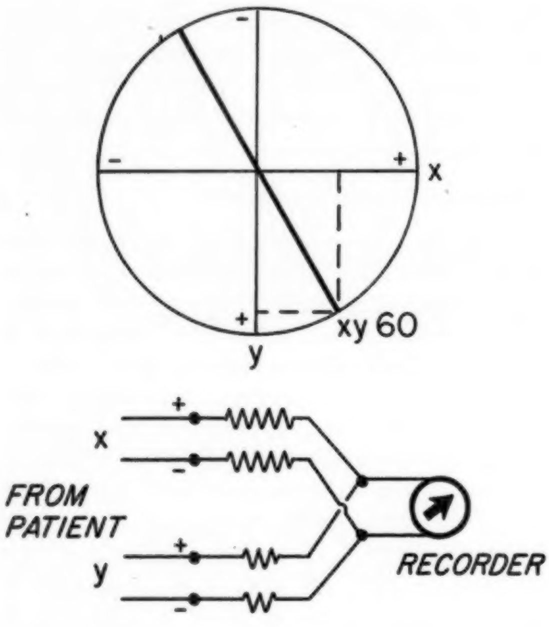

Fig. *1*. Method for resolution of orthogonal leads. Lead XY 60 of the frontal plane (comparable in direction to standard lead II) is shown as example. In the upper diagram this lead is projected on orthogonal leads X and Y. Lead resolution consists of a linear combination of these two leads in proportions equal to the size of the projections. The lower diagram shows the attenuation of leads X and Y to the proportions indicated by the projections. The relatively smaller X value requires larger resistors for lead X but the larger Y value needs less attenuation. The proportions and required resistors are calculated according to: $XY = \pm X \cos \alpha \pm Y \sin \alpha$, where angle α indicates the direction of the desired lead.[23]

writing electrocardiograph* was used for all tracings, using a paper speed of 50 mm. per second. The recording method for the SVEC-III lead system has been reported previously.[22,24] Standard lead I and orthogonal lead X were used as time reference for the two sets of tracings, respectively.

The standard and orthogonal tracings were marked with a code number and then given to two independent readers for analysis and interpretation. Special emphasis was placed on minor detail of the records, such as notching of QRS complexes, T and S-T changes. The abnormal features were listed by each reader, and, finally, an electrocardiographic interpretation was made. Discharge summaries with code numbers for each patient were also available to the interpreters. ECG findings listed in these summaries had been deleted.

*Poly-Viso, Sanborn Company, Waltham, Mass.

The interpreter who read orthogonal records proceeded in the following fashion: At first he analyzed the 3 basic orthogonal leads only and listed his findings. Subsequently, he read the complete set of resolved leads in addition to the 3 basic leads. This was done in order to evaluate the influence of an additional display of data derived from resolved leads. At the end of the study, tracings and readings of both standard and orthogonal leads were compared and listed.

The interpretation of the records was based on a "pattern-type" of analysis commonly used in clinical electrocardiography (Q-wave measurements, incidence of abnormal QS or RSR′ configuration in certain leads, etc.). The correlation, therefore, was essentially based on a pattern comparison. Because of the large variability in direction of effective lead axes of conventional leads,[1] a lead-by-lead correlation between the two sets of compared tracings could not be expected. The search for corresponding patterns, therefore, was always extended over a certain angular range of adjacent leads.

Results

1. Comparison of the 12-lead standard ECG with the 3-lead orthogonal ECG. In 242 out of 261 patients the features which led to electrocardiographic diagnosis in the standard 12-lead ECG could be completely recovered from the 3 orthogonal leads. This represents 92.7 per cent of the total group.

Several types of electrocardiographic abnormalities recognized in the standard leads could not be found in 19 orthogonal 3-lead records. In 8 of these cases with lack of clinical information in orthogonal leads, small R waves with little or no R-wave progression was found in right precordial leads (V_1 to V_3 or V_4). This sequence could not be recognized in the sagittal lead Z. Such findings are frequently labeled as "compatible with loss of anteroseptal electrical forces," although they may also be found in patients with left ventricular hypertrophy, left ventricular conduction defects, and occasionally in normal individuals. Since this feature was not clearly recognized in the orthogonal leads, these 8 cases were counted as deficient in clinical information.

In 4 other cases an RSR′ pattern in

standard lead V_1, without counterpart in the sagittal lead Z, was found. Abnormal Q waves in lead aV_L (0.04 sec. duration and amplitude of 0.2 mv.) were found in 2 additional cases. The closest counterpart of this lead, the horizontal orthogonal lead X, failed to show any Q-wave abnormality. A similar discrepancy was seen in 2 cases with QS waves in leads III and aV_F, without such finding in the vertical lead Y. A further case showed a QS pattern in leads V_1 and V_2, but the sagittal lead Z was of the

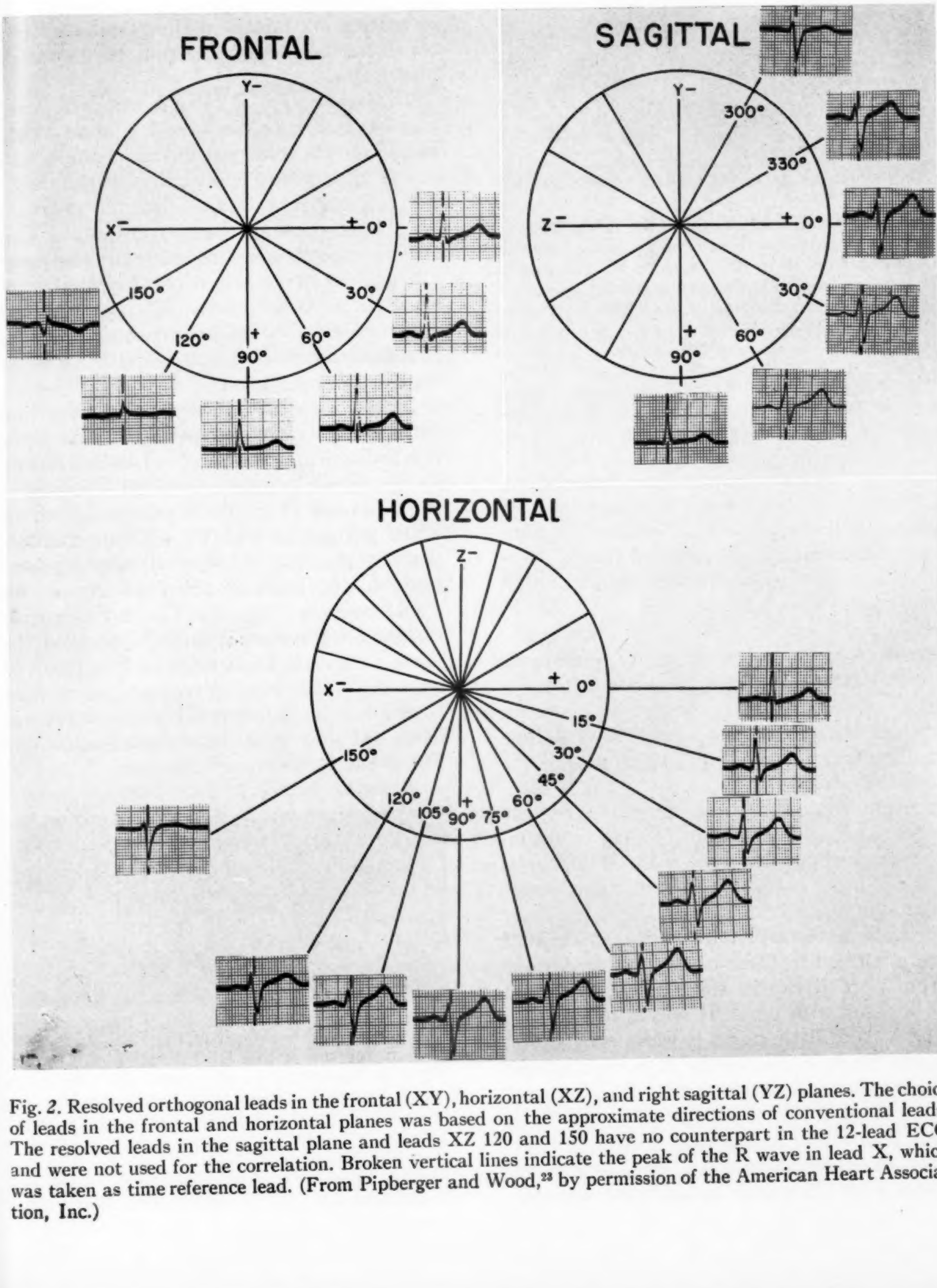

Fig. 2. Resolved orthogonal leads in the frontal (XY), horizontal (XZ), and right sagittal (YZ) planes. The choice of leads in the frontal and horizontal planes was based on the approximate directions of conventional leads. The resolved leads in the sagittal plane and leads XZ 120 and 150 have no counterpart in the 12-lead ECG and were not used for the correlation. Broken vertical lines indicate the peak of the R wave in lead X, which was taken as time reference lead. (From Pipberger and Wood,[23] by permission of the American Heart Association, Inc.)

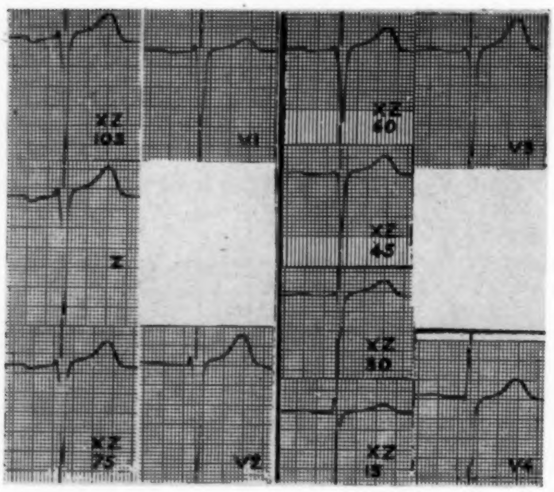

Fig. *3*. Standard leads V_1 to V_3 are of the rS type and do not show any R-wave progression. A sudden transition from rS to RS is seen in V_4. The lack of R-wave progression is also seen in the XZ leads from 105 to 30, with an analogous transition from rS to RS in XZ 15. The orthogonal lead Z of this record was found to be abnormal, with an R/S ratio of less than 0.10. The broken vertical lines in this and the following figures indicate the R-wave peaks in leads X and I which were taken as time reference leads for the two sets of tracings, respectively.

rS type. Another patient's record had QS waves in leads V_3 to V_4. Neither the horizontal lead X nor the sagittal lead Z were found to be abnormal in configuration. A last case showed a so-called "isolated T-wave negativity"[7] in leads V_3 and V_4, i.e., T waves to the right and left of these leads were found to be upright. The orthogonal ECG showed mainly negative T waves both in leads X and Z. The T-wave abnormality, therefore, was not recognized in the orthogonal leads.

After the correlation of patterns the cases with deficiencies in clinical information in orthogonal leads were singled out for further analysis. The preliminary normal standards developed in this laboratory for Schmitt's SVEC-III lead system[25,26] were applied to these cases, and deviations from normal ranges were noted. In 5 out of 8 cases with small R waves in leads V_1 and V_2 and little or no R-wave progression up to leads V_3 or V_4 the R/S ratio of the sagittal lead Z was found to be abnormal (less than 0.10). Such an abnormal ratio was also found in the case with a QS pattern in leads V_1 and V_2. In 2 additional cases with QS waves in leads III and aV_F the determination of the R/S ratio of lead Y resulted in an abnormally low value (less than 0.93). Thus, the application of normal standards for orthogonal leads showed that 8 cases out of 19 with discrepancies in findings were outside normal limits. Even when these cases were discounted, 11 records (4.2 per cent) remained where clinical information contained in the standard ECG could not be recovered from the 3 orthogonal leads.

2. *Comparison of the 12 standard leads with resolved orthogonal leads.* The next step in the correlation consisted in a comparison of the 12 standard leads with resolved leads derived from directions approximately comparable to those of the conventional ECG. In 18 out of 19 cases in which clinically significant detail could not be recovered from the 3 basic orthogonal leads the resolved leads revealed this information. Thus, a complete correlation was found in 99.6 per cent of the total group.

In the 8 cases with small R waves and little or no R-wave progression in the right precordial leads the resolved leads showed an analogous sequence of small R waves in the XZ leads (Fig. 3). In all cases with an RSR′ pattern in lead V_1, without counterpart in the sagittal lead Z, the resolved leads to the right of this lead showed an RSR′ pattern (Fig. 4). The 2 cases with significant Q waves in lead aV_L showed the same pattern in the corresponding resolved lead XY 150. Similar relationships were found in the 2 cases with QS waves in leads III and aV_F. In the case shown in Fig. 5 the R/S ratio of the vertical lead Y,

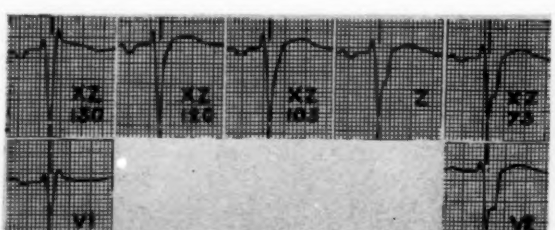

Fig. *4*. Standard lead V_1 is of the RSR′ type. This pattern, together with a QRS duration of 0.14 sec., led to the diagnosis of a right ventricular conduction defect. The characteristic RSR′ pattern is not shown in lead Z. It appears, however, in the resolved lead XZ 150. Note the angular discrepancy in effective electrical directions of leads V_1 and V_2. This has been a frequent finding especially in right precordial leads.

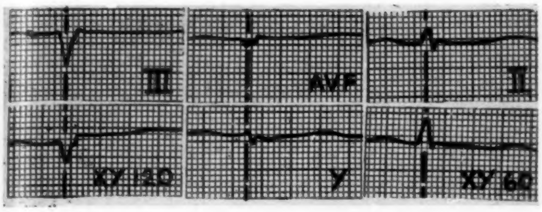

Fig. 5. Standard leads III and aV_F show no initial positivity and are essentially of the QS type (a small terminal R wave can be seen in aV_F). This record was interpreted as compatible with an old diaphragmatic infarct. Orthogonal lead Y shows no Q wave, but its R/S ratio is abnormal (less than 0.93). The resolved lead XY 120 resembles closely lead III, and a similar relationship exists between leads II and XY 60. Note the angular discrepancy between leads aV_F and Y. The transition from a mainly positive to negative deflection lies approximately in the axis of Y. The transition for the standard leads, however, is in between leads II and aV_F, i.e., farther to the left.

as mentioned before, was abnormally low. The resolved lead XY 120, corresponding to lead III, showed the same QS pattern. Both leads II and XY 60 had an RS configuration. It is noteworthy to point out in this case the discrepancy between lead aV_F (QS) and lead Y (rS). The amplitudes in both leads were very low, and both were very close to the transition zone. The standard leads revert from mainly positive deflections to mainly negative ones between leads II and aV_F. A similar transition is seen in the resolved leads, approximately at lead Y or very close to it. Such discrepancies in direction between standard leads and corrected orthogonal leads were found frequently and have been discussed previously.[1,24] They are due to discrepancies between effective electrical lead directions of standard leads and those of corrected leads.

A similar situation was encountered in the case with QS waves in leads V_1 and V_2. The same pattern appeared in the resolved leads XZ 120 and 150 but not in the sagittal lead Z, which showed only an abnormal R/S ratio. The case with QS waves from lead V_3 to lead V_4 showed abnormally small R waves in leads XZ 105 to 45 and no initial R wave in lead XZ 30. Lead Z showed an abnormal R/S ratio in this case (Fig. 6).

The only case out of the total of 261 in which there was an apparent discrepancy in the content of clinical information between standard and resolved leads was the one mentioned previously as having an isolated T-wave negativity in the precordial leads V_3 and V_4 (Fig. 7). T waves of lead Z were biphasic and negative in lead X. Since this is an abnormal finding, the T-wave abnormality by itself would not have been missed in the orthogonal ECG. The reproduction of this T-wave change, however, cannot be considered close enough for a good correlation.

All S-T-segment shifts found in the standard leads were also recovered in the resolved leads (Fig. 8).

Discussion

Although good correlation between findings in the standard 12-lead ECG and resolved leads derived from a corrected orthog-

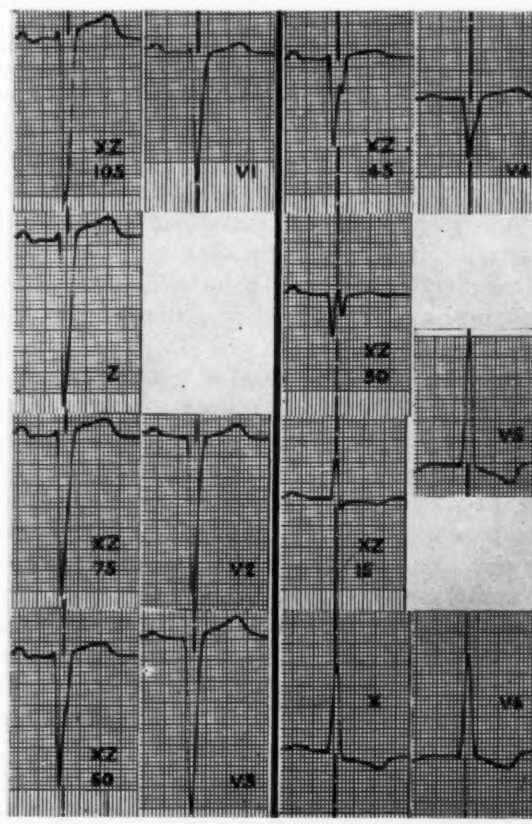

Fig. 6. Standard leads V_1 and V_2 show very small initial R waves, decreasing in amplitude toward the left. Leads V_3 and V_4 are of the QS type. The diagnosis of an old anterior wall infarct was made. Orthogonal lead Z shows an rS pattern with an abnormal R/S ratio of less than 0.10. The resolved leads also lack an R-wave progression toward the left, and in lead XZ 30 the initial R is lost completely. Note the sudden transition from QS in V_4 to R in V_5. The direction of XZ 30 appears to be in between the two.

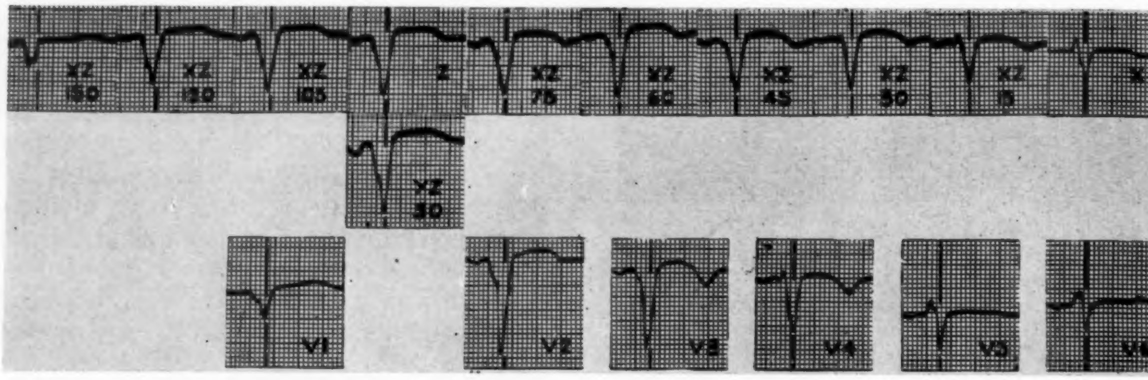

Fig. 7. The T waves in Leads V_3 and V_4 were negative, but mainly positive in the other precordial leads. This was interpreted as an "isolated T-wave negativity." The orthogonal leads show negative T waves over the left precordium (X to XZ 45), becoming biphasic at XZ 60 and mainly positive at XZ 120. The transition zone from positive to negative T deflections is almost parallel to the horizontal XZ level because biphasic T waves are seen over a range of 45 degrees (XZ 60 to 105). Minor deviations in effective electrical direction of standard precordial leads from the XZ level can, therefore, lead to T-wave positivity or negativity. Lead YZ 30, for instance, shows such a discrepancy in the horizontal level. It resembles closely lead V_2, although it is 30 degrees lower than the XZ leads. This record was interpreted as showing an anteroseptal infarct.

onal 3-lead ECG was found in 99.6 per cent of all records, one case in which there was a discrepancy stands out. The significance of the isolated T-wave negativity in leads V_3 and V_4 of this tracing appears debatable, however. As shown in Fig. 7, the T waves were negative in orthogonal lead X and biphasic in lead Z. The resolution of orthogonal leads in the sagittal plane showed an upright T wave 30 degrees below lead Z (YZ 30). This lead resembles very closely standard lead V_2, which displayed a similarly positive T wave. It has to be pointed out that resolved orthogonal leads and standard precordial leads are not necessarily located at the same horizontal level. Furthermore, leads V_3 and V_4 are recorded from an anatomically lower level than leads V_1 and V_2. Discrepancies between directions of anatomic and effective electrical lead axes of standard leads[1,22,27,28] add to the complexity of a correlation lead by lead. Fig. 9 shows another typical example of discrepancies in the horizontal level of different leads. In this case, good correlation was found between leads V_2 and YZ 330, but in this instance, the latter was 30 degrees higher than the horizontal XZ level. Furthermore, Langner and associates[29] have demonstrated that transition zones on the wall of the thorax may follow very irregular patterns. In the case in which there is an isolated T-wave negativity, discrepancies in the horizontal level between leads V_3 and V_4, on the one hand, and the other precordial leads, on the other hand, could easily explain the localized T-wave abnormality. Isolated T-wave negativities, therefore, cannot necessarily serve as evidence for local electrical effects picked up by precordial electrodes from portions of the myocardium underlying the electrode. Further study appears necessary to elucidate the relatively rare finding of isolated T-wave negativity in precordial leads.

In the present study it was found that in 7.3 per cent of all cases, significant diagnostic features of the standard 12-lead ECG could not be recovered in scalar orthogonal 3-lead records. This result compares fairly well with the percentage of 9.8 reported by Abildskov and associates[21] in a similar study on a smaller series. In the present group the number of cases, however, fell to 4.2 per cent when preliminary standards of normalcy[25,26] for orthogonal leads were applied in the analysis. Such a percentage would appear to be still too high to recommend a replacement of the standard 12-lead ECG by 3 orthogonal leads in scalar display.

When *resolved leads* derived from 3 basic orthogonal leads were included in the correlation, there was only one case with a questionable discrepancy in findings. Since resolved leads merely represent a different display of the 3 basic orthogonal leads, no new information not contained in the latter

could have been produced by resolution of the leads. This procedure consists only of linear combinations of the 3 basic orthogonal components, i.e., a special type of transformation of data without derivation of new data from the patient. In this fashion the familiar ECG patterns of the 12-lead ECG can be reproduced, providing identical clinical information. The practically complete correlation between standard and resolved leads indicates, therefore, that discrepancies found in the first comparison with 3 leads only were due to differences in the display of data rather than to deficiencies in the recording of electrical information. It is safe to assume that the display of data in the form of vector loops, which was not included in the present study, would have revealed all of the abnormalities recovered from resolved leads. This is obvious because resolved leads can easily be derived from the conventional 3 plane projections used in vectorcardiography (frontal, sagittal, and horizontal planes).

The good agreement between clinical information derived from the standard 12-lead ECG and the resolved orthogonal 3-lead ECG cannot necessarily be taken as supportive evidence for any hypothesis of a current-generator equivalent, such as the dipole theory. The conventional diagnostic criteria are too crude to be used for such arguments. If the orthogonal leads had suppressed electrical information from the body surface to any appreciable extent, one should have expected, however, considerable discrepancies in findings. A relatively simple generator equivalent such as a dipole, shifting in location during the cardiac cycle,[15,24] could explain the good correlation between standard and orthogonal leads.

From the present large series of patients with ECG abnormalities it can be concluded that the clinical information of the standard 12-lead ECG can only be recovered from a corrected orthogonal 3-lead ECG by resolution of the 3 basic orthogonal components and/or vector loop representation. This indicates that the clinical information is contained in the 3-lead ECG but cannot be recognized without transformation of data. Replacement of the standard 12-lead ECG by a resolved orthogonal 3-lead ECG may not appear to be practical in routine clinical electrocardiography. It has become of major importance, however, in attempts to analyze electrocardiograms automatically by means of electronic computers.[2,3] Reduction of data and elimination of redundant information has to precede computation proper, for technical reasons.[30] Such a sequence is mandatory because of limitations in analog-to-digital conversion facilities and computer memory capacity. Although reduction of data of multichannel analog information such as the 12-lead electrocardiogram can be performed by electronic computers[17] prior to analysis of data, such a sequence is impractical and uneconomical on a large-scale basis. Once the reduced information is stored in the computer memory, however, transformation of data, such as resolution of orthogonal leads, can be performed merely by writing a proper set of instructions for the computer.

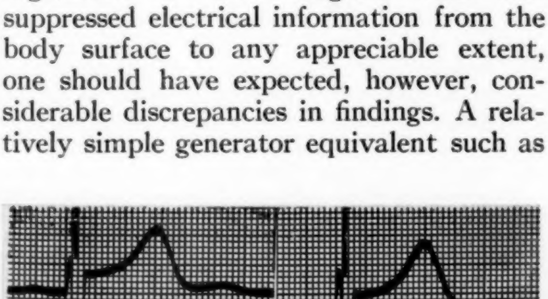

Fig. 8. S-T shift in standard lead V_2 and resolved lead XZ 75. Although minor discrepancies in S-T shifts between standard and orthogonal leads were seen occasionally, all S-T abnormalities were clearly recognized in both sets of tracings.

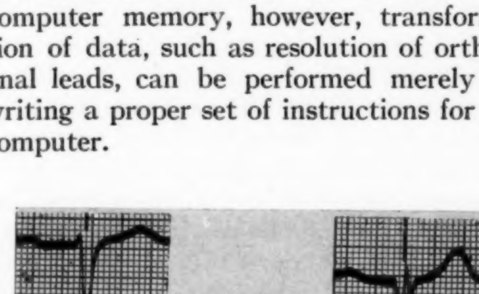

Fig. 9. Similar to Fig. 7, this record illustrates discrepancies in the level of standard precordial and resolved XZ leads. Lead YZ 330 resembles very closely lead V_2, although the former is located 30 degrees above the XZ level.

Since it has been shown that corrected leads exceed conventional bipolar and unipolar leads in constancy of effective lead direction and strength,[1] their greater consistency in performance may enhance the reliability of electrical data recorded from patients. Evidence of superiority in *diagnostic accuracy* of the corrected orthogonal ECG cannot be derived from the present study, however, because the content of clinical information of the conventional 12-lead ECG was used as the only criterion for comparison.

Summary

The clinical information contained in the standard 12-lead ECG was compared with that in the corrected orthogonal 3-lead ECG, in 261 randomly selected patients who showed ECG abnormalities. In a *first correlation*, all electrical information of clinical significance in the 12 standard leads could not be recovered from the 3 orthogonal leads in 7.3 per cent of all cases. In a *second* correlation, orthogonal leads were resolved in order to obtain additional leads from directions comparable to those of standard records. This procedure led to good agreement in all cases except one with a questionable discrepancy. Since lead resolution merely represents a different type of display of the data of orthogonal leads, resolved records do not contain any new information not contained in the 3 basic leads. The conclusion, therefore, was that the informational content of 3 corrected orthogonal leads is comparable to that of the standard 12-lead ECG. Transformation of data, such as orthogonal lead resolution and/or vector loop display, appears to be necessary, however, to recover without appreciable loss the clinical information contained in the standard 12-lead electrocardiogram.

The authors gratefully acknowledge the technical assistance of Miss Marcheta Alion.

REFERENCES

1. Pipberger, H. V.: Current status and persistent problems of electrode placement and lead systems for vectorcardiography and electrocardiography, Prog. Cardiovas. Dis. **2**:248, 1959.
2. Pipberger, H. V., Freis, E. D., Taback, L., and Mason, H. L.: Prepaıation of electrocardiographic data for analysis by digital electronic computer, Circulation **21**:413, 1960.
3. Taback, L., Marden, E., Mason, H. L., and Pipberger, H. V.: Digital recording of electrocardiographic data for analysis by a digital computer, I.R.E. Tr. Medical Electronics ME-**6**:167, 1959.
4. McFee, R., and Johnston, F. D.: Electrocardiographic leads. I. Introduction, Circulation **8**:554, 1953.
5. Helm, R. A.: Theory of vectorcardiography: A review of fundamental concepts, Am. Heart J. **49**:135, 1955.
6. Hartmann, I., Veyrat, R., Wyss, O. A. M., and Duchosal, P. W.: Comparaison vectorielle des électrocardiogrammes unipolaires recueillis en deux points d'un plan transversal, équidistants du centre et opposés par rapport au coeur, Cardiologia **25**:317, 1954.
7. Grant, R. P., and Estes, E. H.: Spatial vector electrocardiography, Philadelphia, 1952, Blakiston Company.
8. Schmitt, O. H., Levine, R. S., Simonson, E., and Dahl, J.: Electrocardiographic mirror pattern studies, Am. Heart J. **45**:416, 500, and 655, 1953.
9. Frank, E.: Measurement and significance of cancellation potentials on the human subject, Circulation **11**:937, 1955.
10. Frank, E.: Critical experiment in electrocardiography, Science **122**:283, 1955.
11. Brody, D. A., and Copeland, G. D.: Electrocardiographic cancellation: Some observations concerning the "nondipolar" fraction of precordial electrocardiograms, Am. Heart J. **56**:381, 1958.
12. Okada, R. H.: Multiple dipole representation of the human heart for vectorcardiography, Science **127**:240, 1958.
13. Morton, R. F., Romans, W. E., and Brody, D. A.: Cancellation of esophageal electrocardiograms, Circulation **15**:897, 1957.
14. Okada, R. H., Langner, P. H., Jr., and Briller, S. A.: Synthesis of precordial potentials from the SVEC III vectorcardiographic system, Circulation Res. **7**:185, 1959.
15. Nelson, C. V., and Hecht, H. H.: Investigation of horizontal components of heart-vector by means of circumferential chest leads at midventricular level, Fed. Proc. **14**:107, 1955.
16. McFee, R., and Parungao, A.: On the interpretation of cancellation experiments. I and II, Am. Heart J. **58**:582, 1959; **59**:433, 1960.
17. Scher, A. M., Young, A. C., and Meredith, W. M.: Factor analysis of the electrocardiogram: A test of electrocardiographic theory. Normal hearts, Circulation Res. **8**:519, 1960.
18. Duchosal, P. W., and Grosgurin, J. R.: The spatial vectorcardiogram obtained by use of a trihedron and its scalar comparisons, Circulation **5**:237, 1952.
19. Milnor, W. R., Talbot, S. A., and Newman, E. V.: A study of the relationship between unipolar leads and spatial vectorcardiograms, using the panoramic vectorcardiograph, Circulation **7**:545, 1953.
20. Frank, E.: An accurate, clinically practical system for spatial vectorcardiography, Circulation **13**:737, 1956.

21. Abildskov, J. A., Street, W. W., Solomon, E., and Toomajian, A. H.: Clinical observations with the Frank precordial lead system, Circulation **17**:1069, 1958.
22. Schmitt, O. H., and Simonson, E.: The present status of vectorcardiography, Arch. Int. Med. **96**:574, 1955.
23. Pipberger, H. V., and Wood, C. R., Jr.: A simplified method for the resolution of the orthogonal electrocardiogram, Circulation Res. **6**:239, 1958.
24. Pipberger, H. V., and Lilienfield, L. S.: The application of corrected electrocardiographic lead systems in man, Am. J. Med. **25**:539, 1958.
25. Pipberger, H. V.: The normal orthogonal electrocardiogram and vectorcardiogram; with a critique of some commonly used analytic criteria, Circulation **17**:1102, 1958.
26. Pipberger, H. V., and Tanenbaum. H. L.: The P-wave, P-R interval and Q-T ratio of the normal orthogonal electrocardiogram, Circulation **18**:1175, 1958.
27. Burger, H. C., and van Milaan, J. B.: Heart vector and leads. I, II, and III, Brit. Heart J. **8**:157, 1946; **9**:154, 1947; **10**:229, 1948.
28. Frank, E.: Spread of current in volume conductors of finite extent, Ann. New York Acad. Sc. **65**:980, 1957.
29. Langner, P. H., Jr., Dewees, E. J., and Moore, S. R.: A critical and comparative analysis of methods in electrocardiography employing mean QRS and T vectors, Am. Heart J. **46**:485, 1953.
30. Pipberger, H. V., and Freis, E. D.: Automatische Analyse kardiologischer Analog-Daten mittels elektronischer Rechenmaschinen, Med. Dok. **4**:58, 1960.

Relation of myocardial bridges and loops on the coronary arteries to coronary occlusions

Přemysl Poláček, Doc., Cand. Sc., MUDr
Hradec Králové, Czechoslovakia

In 1951, a study by Geiringer, entitled "The Mural Coronary," appeared in the *American Heart Journal.*[1] Independently, I began to occupy myself with the same subject. Although there is an extensive literature concerning the course of the coronary arteries, little is known about the relation of their course to the heart muscle. The big stems of the coronary arteries very often disappear under the superficial myocardial fibers for a shorter or longer course and then emerge on the surface of the heart again.

Brief mention of this phenomenon has been made by Reyman,[2] Tandler,[3] Crainicianu,[4] and Djavakhishvili and Komakhidze.[5] The only authors who occupy themselves with the subject are the above-mentioned Geiringer,[1] who distinguishes the "mural" and the "epicardial" courses of the artery, and Edwards, Burnsides, Swarm and Lansing.[13] Recently, Porstmann and Iwig[6] diagnosed this intramural stretch of the coronary artery in a patient by means of serial coronariogram.

Because these muscular fibers which lie upon the artery might have an influence on the passage of the blood through the artery, our first study was based upon the macroscopic appearance and occurrence of these muscular overbridgings.[7,8] Further study concerned their relationship to some physical marks,[9] and, finally, their microscopic relationship to the wall and structure of the artery.[10,11] The present work is a summary of our up-to-date experience.

Materials and methods

The observations are based upon a detailed preparation of the coronary arteries of 70 hearts of persons who ranged in age from newborn to 80 years. In more than half of the cases the coronary arteries were filled with colored gelatin in order to make their course more distinct.

A microscopic study of sections from 36 hearts was undertaken; staining was done with hematoxylin-eosin, after van Gieson and with green trichrome, which proved to be the best for our purpose.

In order to determine the thickness of the intima, the magnified sections were drawn on paper of constant thickness (0.28 μ), and by weighing the whole wall of the artery and then the intima, we ascertained what proportion the intima comprised of the whole wall of the artery. The other way to determine the thickness of the intima was the direct micromeasurement of minimum and maximum thickness of it in all sections. Both of these methods gave the same results as to the proportion of the thickness of the intima and the wall of the artery, i.e., they gave the picture of the degree of hyperplasia of the intima. The latter method allowed the study of the degree of inequality of this hyperplasia.

From the Department of Anatomy, Charles University Medical Faculty, Hradec Králové, Czechoslovakia.
Received for publication May 31, 1960.

Macroscopic findings

The muscular formations which overbridge the arterial course exist in two forms, viz., muscular bridges and muscular loops.

Bridges occur in the course of the coronary arteries over the ventricular myocardium. They can be seen after the removal of subepicardial fat tissue (Fig. 1). The artery often dips under the superficial layer of ventricular myocardium, and after a shorter or longer course under the muscle it appears on the surface again. The length of such a muscular bridge may be 3 to 69 mm.; most often, however, it is 20 to 30 mm. In some cases the muscular fibers may lie very close on the adventitia of the artery, whereas in other cases there is interstitial fat tissue between the bridge and the adventitia (Fig. 3). The thickness varies up to 5 mm.

The muscular loops occur in the course of arteries in the atrioventricular groove (Fig. 2). They are formed by muscular fibers of the atrial myocardium, which vault from the wall of the atrium, embrace the artery up to three fourths of its wall circumference, and then return into the atrial myocardium (Fig. 4). In all cases they have a close relation to the adventitia of the artery, and their length is 2 to 30 mm., most often 10 to 15 mm. They are thinner than the muscular bridges, and, therefore, their preparation is more difficult. Their thickness is 100 to 300 μ.

In 70 hearts we found a total of 167 muscular overbridgings, among them 108 bridges and 59 loops. The greatest number of these formations in one heart was 6. In only 10 hearts were none of the muscular formations observed. These formations are bound to certain places, where they have a certain frequency of occurrence (Fig. 5). The most frequent place of occurrence is the proximal half of the anterior descending branch of the left coronary artery during its course in the interventricular groove; the muscular bridge in this location appears in 60 per cent of all cases. In this locality, bridging may also be doubled, but rarely tripled. The other branches are overbridged less often: the oblique branch of the left coronary artery in 18.5 per cent, the marginal branch in 14.2 per cent, and the terminal branches of the left coronary artery on the diaphragmatic heart surface in no more than 7.1 per cent of the cases.

The most frequent place of occurrence of the muscular loop is in the course of the circumflex branch of the left coronary artery in the atrioventricular groove, where the artery curves the obtuse margin. Here the occurrence is 40 per cent.

The left coronary artery and its branches possess the muscular formations in 77.1 per cent of the cases, whereas the right coronary artery is overbridged less frequently, i.e., in only 41.4 per cent. The difference becomes still more striking by a comparison of the whole number of the muscular formations found. Of 167 of them, there were 121 in the region of the left coronary artery (72.5 per cent) and 46 in the region of the right coronary artery (27.5 per cent).

The right coronary artery in the atrioventricular groove is embraced by muscular fibers, too; however they are weaker and shorter. They occur less frequently on the curve of the artery over the acute margin (in only 8.5 per cent of the cases); occurrence is more frequent in the terminal part where the artery is crossed by the medial heart vein, after it has given off its posterior descending branch. There the loops are present in 27.1 per cent of the cases as the most frequent muscular formation in the region of the right coronary artery, and as the third most frequent location in the heart as a whole. Thus, loops overbridge the terminal branches of the right coronary artery which supplies the posterior part of the left ventricle.

The muscular bridges of the branches of the right coronary artery are rarer and more variable in their form and location; they are found in 2.8 to 11.4 per cent of the cases.

Microscopic findings

A close relationship of muscular fibers to the adventitia of the artery can be observed very often in bridges, but always in loops. In some cases, even transition of the joints of muscular fibers into fibrous tissue of the adventitia can be observed, or the muscular fibers run directly into the adventitia in a certain stretch of the artery.

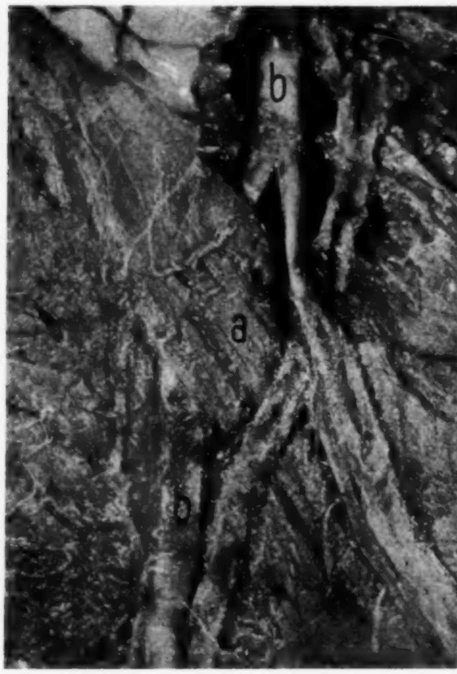

Fig. *1.*

Fig. *2.*

Fig. *1.* Muscular bridge (*a*) on the anterior descending branch of the left coronary artery (*b*).

Fig. *2.* Muscular loop (*a*) on the right coronary artery (*b*).

Muscular fibers of the described formations run mostly in the same direction and usually cross the artery obliquely. In loops it was possible to observe, in some cases, two layers of muscular fibers (circular and longitudinal); in one case there were even three layers.

In older persons the muscular loops could change: the muscular tissue was transformed into collagen tissue. In such a fibrous loop the muscular tissue is preserved only in some places.

Furthermore, we concerned ourselves with the influence of the muscular formations (especially the most frequent formation, i.e., the bridge on the anterior descending branch of the left coronary artery) on the media and the intima of the artery.

The thickness of the media in 14 cases observed comprised 20 to 40 per cent of the whole wall of the artery before the bridge, 25 to 50 per cent under the bridge, and 30 to 45 per cent behind the bridge. Thus, it comprises approximately one third of the thickness of the wall of the vessel in all three stretches observed and does not vary essentially.

Interesting differences can be observed in the intima (Table I). Before the bridge it occupied 33.8 per cent of the surface of the section, under the bridge, only 20.6 per cent, and behind the bridge, 22.9 per cent in our 14 cases. The difference of the surface before and under the bridge appears to be statistically significant. Also the relationship between the minimum and maximum thickness of the intima is similar. Before the bridge the intima makes up 22.8 to 54.6 per cent of the wall of the artery, whereas under the bridge it makes up only 13.0 to 35.8 per cent, and behind the bridge, 17.1 to 36.7 per cent. In the stretch of the artery before the bridge the intima is, thus, much thicker than under the bridge, whereas behind the bridge it is of the same thickness or a little thicker.

Most important, however, is the comparison of the same stretches of a bridged and unbridged artery before the bridge (Table II). We examined 8 unbridged and 16 bridged arteries. The surface measurements gave the same results in both instances: in the unbridged artery the surface of the intima was, on the average, 35.9 per cent of the whole wall of the artery,

and in the bridged artery it was 35.6 per cent. But a quite different result was obtained by a comparison of the minimum and maximum values of the thickness of the intima, in per cent, of the whole wall. In the unbridged artery the average minimum was 33.5 per cent, and the average maximum was 47.9 per cent; in the bridged artery the average minimum was 26.0 per cent, and the average maximum was 56.8 per cent. In the bridged artery the minimum value was lower, whereas the maximum value, on the other hand, was higher. If the difference between the minimum and maximum is only 14.4 per cent in an unbridged artery, in a bridged artery it is as much as 30.8 per cent. The statistical evaluation of these differences shows a high significance. From this it follows that hyperplasia of the intima in a bridged artery before the bridge shows a much greater irregularity than in an unbridged artery at the same level. The same result gives measurement of the thickness of the intima of the bridged anterior descending branch of the left coronary artery and of its unbridged oblique branch before the bridge (Table II); both arteries were visible in one and the same section. In all of the 7 cases observed the difference between the minimum and the maximum thickness of the intima was greater in the bridged descending branch (34.4 per cent) than in the unbridged oblique branch (17.8 per cent). In this case, too, the difference is close to the limit of statistical

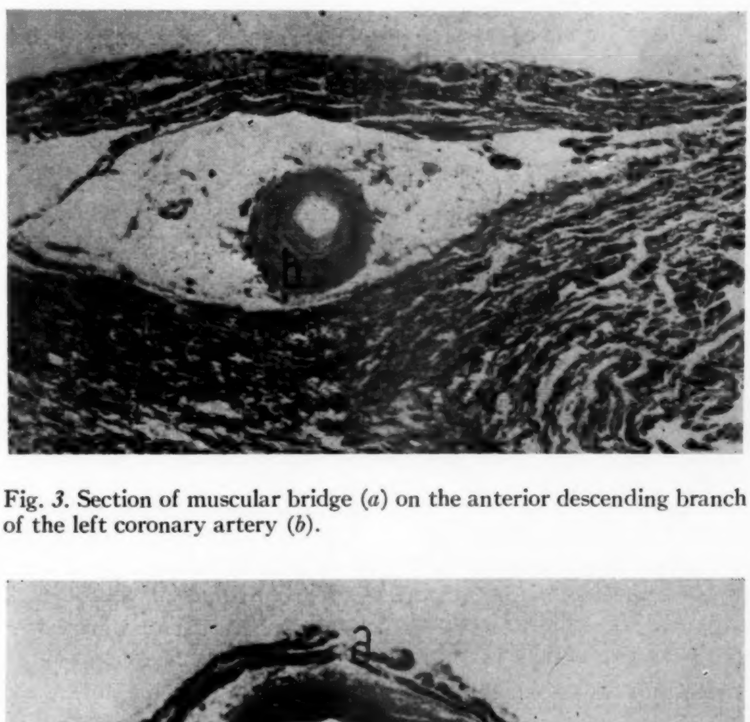

Fig. *3*. Section of muscular bridge (*a*) on the anterior descending branch of the left coronary artery (*b*).

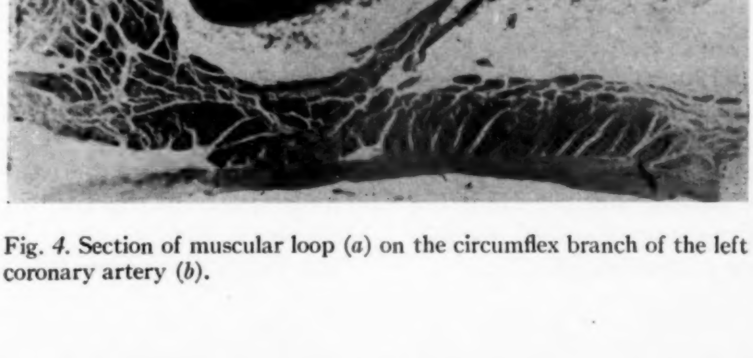

Fig. *4*. Section of muscular loop (*a*) on the circumflex branch of the left coronary artery (*b*).

Table I. *Anterior descending branch of the left coronary artery. The thickness of the intima, in per cent, of the whole wall*

	Number of cases	*Minimum-maximum thickness (arithmetic average)*	*Difference between minimum and maximum*	*Surface (arithmetic average)*	*Statistical significance of differences in the surfaces (t-test after Fisher)*
Before the bridge	14	22.8–54.6	31.8	33.8	$t = 3.06$ $p < 0.01$
Under the bridge	14	13.0–35.8	22.8	20.6	Statistically insignificant
Behind the bridge	14	17.1–36.7	19.6	22.9	

Table II. *Bridged and unbridged coronary artery. The hyperplasia of the intima, in per cent, of the whole wall in the stretch before the bridge*

	Number of cases	*Surface (arithmetic average)*	*Minimum-maximum thickness (arithmetic average)*	*Difference between minimum and maximum*	*Statistical significance of differences between minimum and maximum (t-test after Fisher)*
Unbridged anterior descending branch	8	35.9	33.5–47.9	14.4	$t = 2.98$ $p < 0.01$
Bridged anterior descending branch	16	35.6	26.0–56.8	30.8	
Bridged anterior descending branch	7	—	23.2–57.6	34.4	$t = 2.59$ $p < 0.05$
Unbridged oblique branch	7	—	29.3–47.1	17.8	

significance, although the number of cases is very small.

Schematically demonstrated (Fig. 6), the bridge effects the unequal hyperplasia of the intima in the proximal stretch of the artery, whereas on the distal stretch it has no influence; here the artery behaves in the same manner as do other arteries lying subepicardially.

Especially interesting was one case in which the anterior descending branch divided into three branches (trifurcation), and each of these branches had a different course (Fig. 7). The sclerotic obliterated artery (*1*) entered under a very big bridge, the artery with unchanged intima (*2*) had only a subepicardial course, and the artery with moderately thickened intima (*3*) dipped under a smaller bridge. Here the fate of the intima corresponded exactly with the presence of the bridge.

Discussion

In the literature the frequency of the overbridgings is mentioned by Geiringer[1] in the anterior descending branch of the left coronary artery, where the author found the bridge in 23 out of 100 cases. In our material, a bridge occurred in 60 per cent of the cases at the place mentioned: this is a much higher incidence. Edwards, Burnsides, Swarm and Lansing[13] found the overbridgings in 5.4 per cent of all hearts (15 times in 276 hearts). Djavakhishvili and Komakhidze[5] observed these formations in half of all hearts observed, whereas in our material they were found in 85.7 per cent of the cases. We could confirm the observation of these latter authors that these formations are more frequent in the region of the left coronary artery than in the region of the right one. The muscular loops have

not yet been described in the literature.

It is known in regard to the coronary arteries that the most frequent occlusions occur, in the first place, in the proximal part of the anterior descending branch of the left coronary artery, in the second place, in the proximal stretch of the circumflex branch of the left coronary artery before the obtuse margin, and, in the third place, in the terminal stretch of the right coronary artery, at the origin of its posterior descending branch (Koch and Kong[12]). These places correspond to the stretches of the arteries before the sites of the most frequent occurrence of muscular overbridgings, even in the same succession.

No difference was found in the occurrence of the bridges and loops in different age groups. This fact means that these formations are already present in newborn infants, and, on the basis of our own sections, they are present even in the fetus. They develop as early as the embryonic period, at the time of the formation of the coronary arteries from the original capillary network. This opinion we share with Geiringer.[1] In agreement with him, we find no differences between the sexes. Nevertheless, there is some tendency to a greater number of overbridgings in the region of the left coronary artery in men than in women (82.5 to 70.0 per cent).[9]

Furthermore, we find some relation of the muscular formations to the length of body and to the physical type. In tall and thin persons the muscular bridges and loops are more frequent in the region of the left coronary artery than they are in short and thick persons. On the contrary, in the region of the right coronary artery the overbridgings appear more often in short and thick persons than in tall and thin persons.[9]

From the autopsy records of the Institutes of Forensic Medicine and of Pathologic Anatomy of our Medical Faculty

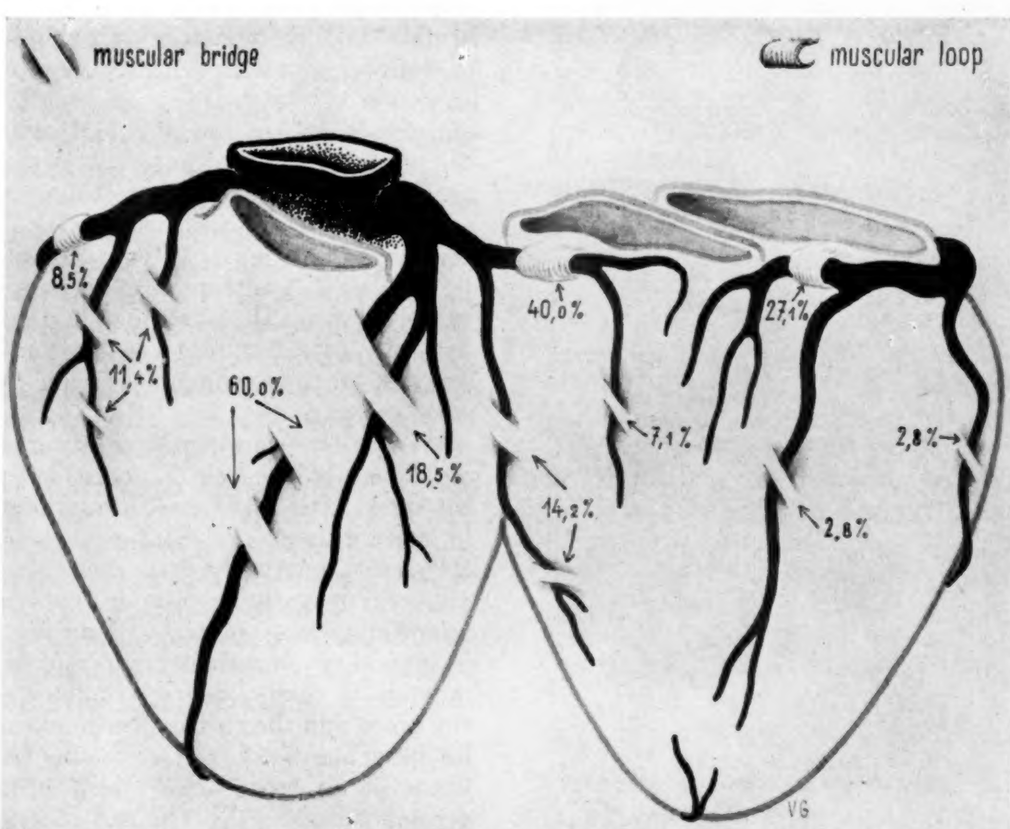

Fig. 5. Occurrence of muscular bridges and loops on the coronary arteries, in per cent. (Drawn by V. Gabrielová.)

we ascertained that anterior myocardial infarction really occurs more often in tall and thin persons, whereas posterior myocardial infarction is relatively more frequent in short and thick persons.

The clue to these coincidences between the described muscular formations and occlusions of coronary arteries is given in the results of microscopic study. In agreement with Geiringer,[1] we state that the bridge does not affect the media of the artery, but it affects its intima. Diffuse hyperplasia of the intima, as a manifestation of the aging of the vessel, becomes more and more intensive during the growth. The bridge affects the intima favorably in that direction, in that it hinders this hyperplasia. We observed this phenomenon by two methods other than Geiringer's, and can therefore confirm his observation that the intima in the subepicardial stretches of the artery is

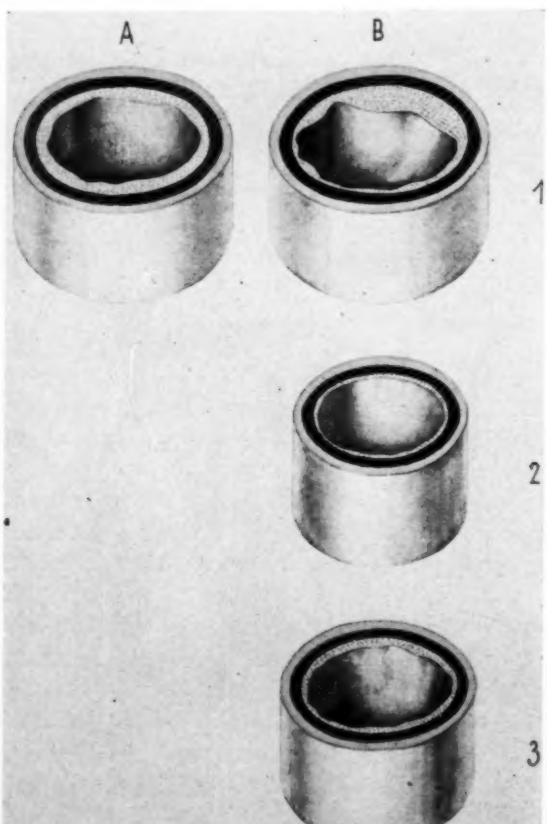

Fig. 6. Thickness of the intima in an unbridged (*A*) and bridged (*B*) anterior descending branch of the left coronary artery before (*1*), under (*2*) and behind (*3*) the bridge. (Drawn by V. Gabrielová.)

hyperplastic, whereas in the "mural" stretches (i.e., under the bridge) it remains thin. On the other hand, we could not agree with the findings of Edwards, Burnsides, Swarm and Lansing,[13] who did not observe any difference between the sclerotic process in the "intramural" (i.e., under the bridge) and that in the "extramural" (i.e., subepicardial) portions of the coronary arteries.

But first of all, we aimed at the difference between the bridged and unbridged artery in that stretch in which occlusions most often occur. Even if the degree of intimal hyperplasia is the same in both cases, there is a marked difference in the form of this hyperplasia. In an unbridged artery the hyperplasia is more regular, whereas in a bridged artery it is strongly irregular—the thin places of the intima alternate with hyperplastic intima, and sclerotic plaques are formed. Irregular hyperplasia could be observed even in a 15-year-old person in our material. This finding can be explained by the effort exerted by the wall before the bridge, in connection with the constriction of the artery in systole, which is evident from the observation of Porstmann and Iwig.[6] These authors found, in the proximal stretch of the course of the anterior descending branch, rhythmical constrictions of the artery in every systole during the serial coronariogram in a 19-year-old patient. In this way, a site of predilection is developed (one of the morphologic conditions for the manifestation of the sclerotic process) for the forming of sclerotic plaques and occlusions.

We are far from considering the bridges and loops as a cause of occlusions of the coronary arteries. These formations exist in most persons (in 85.7 per cent), and they exist, on the basis of our own observations, in various animals, even if the sclerotic process of the coronaries which is typical of man does not occur in these animals to such a degree. In the heart of the horse and the cow the coronary arteries lie subepicardially, but only the terminal branches of second and third order are occasionally bridged. On the contrary, in the rabbit, guinea pig, and rat the arteries run intramurally from the beginning. The same conditions found in man are found

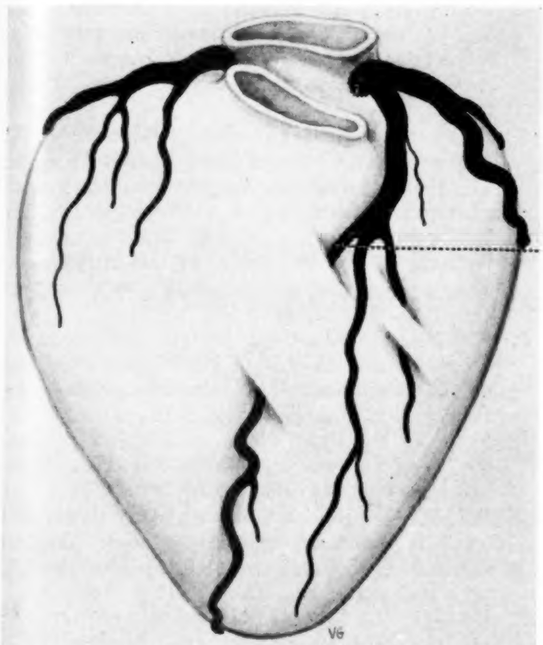

Fig. 7.

Fig. 7. Section through the anterior descending branch of the left coronary artery and its branches. See text for explanation. (Diagram on left by V. Gabrielová.)

in the dog, and especially in macaques. In sheep and goats the subepicardial and myocardial stretches of the artery alternate even more often than in man, and the number of bridges and their size are much greater.[10] In spite of this fact, these animals do not suffer from such a sclerotic process of the coronaries and from myocardial infarctions as are known in man.

Schematically formulated, the proper cause of the sclerotic process lies in the changes of metabolic processes under the influence of some not yet quite well-known noxious effects, which manifest themselves as hyperplasia of the fibrous tissue or as lipoid infiltration of the intima. The bridges and loops, however, form a suitable morphologic condition for the development of this process. Only in this way can we explain the striking relationship between the localization of the most frequent occlusions of the coronary arteries and the stretches of the artery behind which the described formations occur most often.

Summary

1. The muscular overbridgings on the coronary arteries of 70 human hearts are described and classified into (a) muscular bridges under which the artery submerges during its course over the surface of the ventricles, and (b) muscular loops which attach the artery to the atrial myocardium during its course in the atrioventricular groove. These formations occur in 85.7 per cent of all hearts; the occurrence is more frequent in the region of the left coronary artery.

2. The muscular bridges formed by ventricular myocardium—usually 10 to 20 mm. long, up to 5 mm. thick, and rarely mentioned in the literature—are most frequent in the proximal half of the anterior descending branch (60.0 per cent), next most frequent in the oblique branch of the left coronary artery (18.5 per cent), and rarer (2.8 to 14.2 per cent) in other branches of the left and right coronary arteries.

3. The muscular loops, formed by atrial myocardium—usually 10 to 15 mm. long, 100 to 300 μ thick, and not mentioned in the literature up to now—are most frequent in the first stretch of the circumflex branch of the left coronary artery (40.0 per cent), and in the terminal stretch of the right coronary artery (27.1 per cent).

4. The stretch of the artery before the bridge or loop corresponds to the sites at which occlusions most frequently occur, just as the order of frequency is the same as that of the occurrence of these formations (the origin of the anterior descending branch, the proximal stretch of the circumflex branch of the left, and the terminal stretch of the right coronary arteries).

5. Microscopic examination of 36 hearts showed a very close relationship of the muscular formation to the adventitia.

The muscular overbridging may have more layers (circular and longitudinal). In the muscular loops, fibrous degeneration in old persons was observed to greater or smaller degree.

6. The intima of the artery under the bridge is normally thin, whereas especially before the bridge it is strongly hyperplastic, but sometimes also behind the bridge.

7. The degree of hyperplasia of the intima in unbridged and bridged arteries before the bridge (most frequently the site of occlusions) is compared. As to the surface of the sections, hyperplasia of the intima is of the same degree, but there is a difference in its shape. Hyperplasia of the intima in the unbridged artery is more regular, whereas in the bridged artery it is irregular, and there is a greater tendency to the formation of sclerotic plaques.

8. The stretches of the arteries before the muscular bridges and loops could become one of the morphologic conditions, a site of predilection, for a sclerotic process. In this way the coincidence between sites of the most frequent overbridgings and those of the most frequent occlusions of the coronary arteries could be explained.

REFERENCES

1. Geiringer, E.: The mural coronary, Am. Heart J. **41**:359, 1951.
2. Reyman, H. Ch.: Dissertatio de vasis cordis propriis, Haller, Biblioth. anat. **2**:366, 1737.
3. Tandler, J.: Anatomie des Herzens, Jena, 1913, Fischer, p. 220.
4. Crainicianu, A.: Anatomische Studien über die Coronararterien und experimentelle Untersuchungen über ihre Durchgängigkeit, Virchows Arch. f. path. Anat. u. Physiol. **238**:1, 1922.
5. Djavakhishvili, N. A., and Komakhidze, M. E.: Applied morphology of heart vessels (Russian Text), Tezisy dokladov VI. vsesoyuznogo syezda anatomov, gistologov i embriologov, Kijev 565, 1958.
6. Porstmann, W., and Iwig, J.: Die intramurale Koronarie im Angiogramm, Fortschr. Röntgenstr. **92**:129, 1960.
7. Poláček, P.: Muscular bridges and loops on coronary arteries of man (Czech text), Sdělení na II. konferenci Čs. morfologů—Smolenice 1958. Čs. morfologie **7**:119, 1959.
8. Poláček, P.: Über die myokardialen Bündel, die den Verlauf der Koronararterien überbrücken, Anat. Anzeiger **106**:386, 1959.
9. Poláček, P.: Relation of muscular bridges and loops on coronary arteries to some physical marks in man (Czech text) Sborník lékařské fakulty KU v Hradci Králové **1**:40, 1960.
10. Poláček, P.: Myocardial bridges and loops on the coronary arteries in man. Abstract from inaugural dissertation (Czech text). Sborník lékařské fakulty KU v Hradci Králové—Supplementum **2-3**, 1960 (in press).
11. Poláček, P.: Microscopical observation of the muscular bridges and loops on the human coronary arteries (Czech text). Čs. morfologie, **8**:345, 1960.
12. Koch, W., and Kong, L.Ch.: Über die Formen des Coronarverschlusses, die Änderungen im Coronarkreislauf und die Beziehungen zur Angina pectoris, Beitr. z. path. Anat. u.z. allgem. Pathol. **90**:21, 1932.
13. Edwards, J. C., Burnsides, Ch., Swarm, R. L., and Lansing, A. I.: Arteriosclerosis in the intramural and extramural portions of coronary arteries in the human heart, Circulation **13**:235, 1956.

Hydrogen-platinum electrode system in detection of intravascular shunts

Albert L. Hyman, M.D.
Edward S. Hyman, M.D
*Antonio C. Quiroz, M.D.**
*James R. Gantt, M.D.**
New Orleans, La.

Recent advances in cardiovascular surgery have emphasized the need for more accurate techniques in preoperative diagnosis of cardiac abnormalities. The limitations of the oxygen method in this study of shunts are well known. More accurate techniques employing the indicator-dilution principle have been developed.[1-3]

Recently, Clark[4] described a method of labeling blood in the lung by means of hydrogen inhalation. As it reaches the right heart, the hydrogen-labeled blood is detected by a change in oxidation potential, as registered by the platinum electrode at that site. The present report describes a modification and extension of the Clark technique with studies in 34 patients in whom intravascular shunts were confirmed or suspected. In addition, the comparative sensitivity of the hydrogen, dye-dilution, and oxygen methods was evaluated in 5 dogs with subclavian-pulmonary arterial anastomoses.

Methods and materials

Electrodes. Standard Goodale No. 5 and 6 intracardiac catheters were modified in order to introduce a shielded, insulated conductor to an exposed platinum tip without occluding the side holes or affecting the autoclavability of the catheter. A bead made at the tip of a piece of platinum wire was spot-soldered to a length of No. 32-41 polyurethane insulated magnet wire.† The bare metal was dipped in epoxy resin‡ and baked to complete the insulation. The wire was then drawn through the catheter from tip to butt and through the wall of the catheter near the butt end with a sewing needle. Epoxy resin was applied to seal the bead in the tip and the hole in the catheter wall. During baking, the conductor was displaced from the side holes by a Teflon plug. The wire which penetrated the wall of the catheter was soldered to the center conductor of a subminiature, Teflon-insulated coaxial cable§ which was 3 to 4 inches in length. This solder junction was insulated with epoxy. The shield from the cable was wrapped around the catheter. Nylon thread was wound around the junction, and a solution of polyvinyl chloride was applied, fusing the junction to the wall of the catheter. A subminiature, gold-plated, Tef-

From the Departments of Medicine and Surgery, Tulane University School of Medicine, Charity Hospital of Louisiana, and the Department of Biophysics, Touro Infirmary, New Orleans, La.
Supported by grants from Louisiana Heart Association and U. S. Public Health Service.
Received for publication June 21, 1960.
*Trainee, National Heart Institute, National Institutes of Health, U.S.P.H.S. Grant No. HTS5170.
†General Cable Corp., Bayonne, N. J.
‡Products Research Corp., Belle Chasse, La.
§Amphenol No. RG 188/μ.

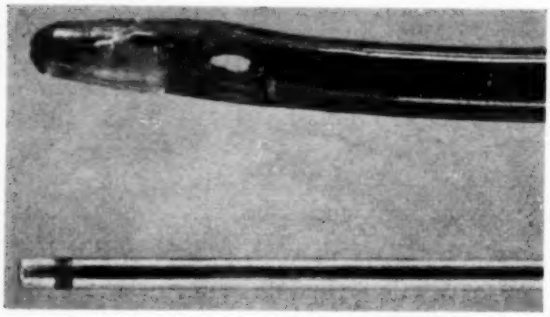

Fig. *1*. Catheter tip, demonstrating position of platinum bead and epoxy resin, with maintenance of lateral openings. Stylet tip for Cournand intra-arterial needle indicating platinum tip with epoxy insulation band.

lon-insulated connector* was attached to the free end of the cable. An autoclavable extension was made of the same cable and connectors. The platinum tip was exposed and shaped with a jeweler's file. The platinum electrode was blacked by cathodizing briefly in a chloroplatinic acid solution (Fig. 1).

Probes for Cournand and Henry needles were similarly constructed. A bead was formed on an appropriate length of platinum wire which had been pulled to 30-F gauge for the Cournand needle and 41-F gauge for the Henry needle. This length was insulated by several thin applications of epoxy or polyurethane resin. It was then inserted through epoxy-filled stainless steel tubing. The resin was polymerized, fixing the platinum. The tip of platinum wire was spot-soldered to the coaxial cable, epoxy insulated, and covered with the shield which was embedded in an epoxy bead. This bead rigidly fixed the cable to the stainless steel tubing. The protruding platinum bead was shaped with a jeweler's file and burnishing tool to conform to the shape of the needle tubing. The protrusion of the probe tip beyond the shell of the outer needle was adjusted by a Teflon spacer (Fig. 2).

Electrical circuit. Adequate measurement of oxidation potentials requires a higher impedance device (in order to avoid loading the half cell) than is found in most recording instruments which have an input impedance of about 1 megohm. A simple, one tube per channel, battery-operated, DC-coupled cathode follower circuit with an input impedance of 22 megohms was constructed (Fig. 3). Although this circuit had a voltage amplification of less than unity (approximately 0.6), the resultant signals were larger because of reduced loading. This also makes the signal less dependent on the size of the electrode (Fig. 4). A standard calomel-saturated KCl electrode was used as a common reference and was simply wrapped in gauze, taped to the skin of the patient, and wet with saline.

Clinical studies. Thirty-four patients were studied with the hydrogen electrode, the double-catheter dye-dilution, and oxygen techniques. The platinum-tipped catheter was passed from an arm vein into the pulmonary artery. The platinum-tipped stylet was inserted through an intra-arterial needle, and proper electrical connections were made by means of sterile extension cords. A platinum- or rhodium-plated nosepiece was taped in place on the nasal mucosa. The patient took one breath of hydrogen, and the changes in oxidation potential were monitored and recorded as continuous curves on an eight-channel recorder.* The presence of a left-to-right shunt was readily detected from the early appearance of hydrogen in the right heart or pulmonary artery, as compared with the time of appearance in the femoral artery. Pressure was simultaneously recorded. Approximately 2 to 4 minutes were required for the curves to return to the base line. This procedure was repeated in each chamber of the right heart in order to localize the shunt.

Two patients with pulmonary stenosis and atrial septal defect and 1 patient with ventricular septal defect had right-to-left shunts. These patients were studied after rapid manual injection of 10 to 15 c.c. of blood or saline which had been exposed to hydrogen for 2 to 3 minutes. The labeled blood or saline was injected into a cardiac catheter which had been placed upstream from the site of the right-to-left shunt, and the hydrogen was detected by the electrode stylet in the systemic artery. Similar studies were performed by means of injection of Cardiogreen dye, with

*Amphenol No. 27—7; 27—8.

*Electronics for Medicine, White Plains, N. Y.

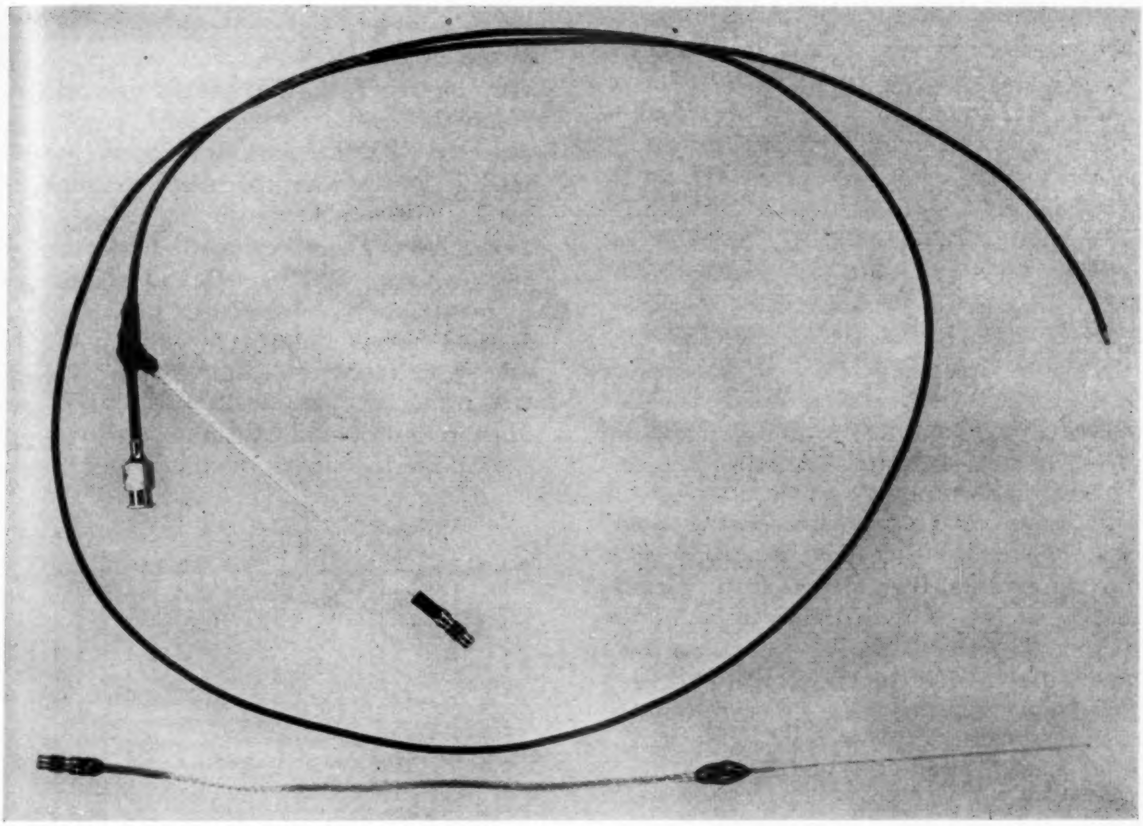

Fig. 2. Cardiac catheter and intra-arterial stylet with platinum electrodes in tips.

detection of the appearance of the characteristic two peaks in the systemic arterial curve.[5]

Experimental studies. The left subclavian artery was anastomosed to the pulmonary artery in 5 mongrel dogs. A Jacobson inflatable cuff was placed about the subclavian artery, and the injection arm was implanted subcutaneously. Approximately 2 weeks after recovery the animals were studied under intravenous Nembutal anesthesia and endotracheal intubation. A No. 5 or 6 Goodale catheter with a platinum-tipped electrode was passed into the left pulmonary artery. A second No. 6 Goodale catheter without an electrode was passed into the same position. Another No. 6 Goodale catheter was then passed into the right ventricle. A Cournand needle was placed in the femoral artery. The cuff which had previously been inflated with 2 to 3 c.c. of water to completely occlude the shunt was deflated in stages, removing 0.05 c.c. at a time until the hydrogen-platinum system detected a shunt. The platinum electrode catheter was then carefully passed peripherally to avoid disturbing the other two catheters. Dye curves were obtained from the pulmonary artery and femoral artery after injection of 1.25 mg. of indocyanine dye into the platinum electrode catheter, which had been placed in a peripheral pulmonary artery. The calibration of the pulmonary curve was such that a deflection of 1 cm. equaled 0.017 mg. of Cardiogreen dye per liter of blood. Blood was also withdrawn from the left pulmonary artery and right ventricle for analysis of oxygen content. A shunt was considered to be present when the difference in oxygen between the sample from the pulmonary artery and that from the right ventricle was 0.5 volume per cent.[6] The cuff was then deflated stepwise until both methods indicated the presence of a shunt. The relationship of the appearance of a shunt in these methods and the appearance of the murmur was noted. The femoral arterial pressure was not altered during the procedure.

In one dog a platinum electrode catheter was passed into the pulmonary artery

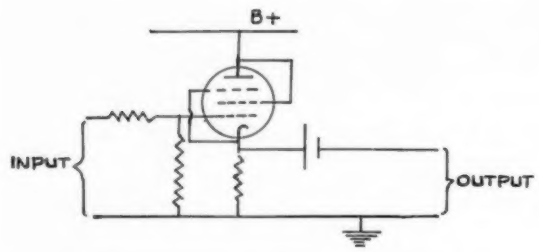

Fig. 3. Diagram of electrical circuit for high impedance.

from a neck vein, and a No. 6 Goodale catheter was passed from the femoral artery retrograde into the left ventricle. The cardiac output was measured by the Fick method. Hydrogen-saturated blood was injected at successively slower rates into an external jugular vein until it could just be detected by the electrode in the pulmonary artery. Similar injections were made into the left ventricle until hydrogen could just be detected by the femoral electrode.

Results

Detection of shunts in patients. The hydrogen-platinum system detected a left-to-right shunt in every instance in which the dye technique indicated the presence of this shunt. Typical curves are shown in Figs. 5 through 8. In 4 patients with smaller shunts (less than 0.5 times the systemic blood flow) the oxygen method gave equivocal or negative results. The hydrogen-platinum system did not detect a left-to-right shunt in any of the patients when the dye method failed to indicate its presence.

In 2 of the 3 patients with right-to-left shunts the hydrogen-platinum and the dye systems correctly detected the site of the right-to-left shunt. In the third, a patient with pulmonary stenosis and atrial septal defect, the dye and oxygen methods detected a small shunt (less than 15 per cent of the systemic venous return), although the hydrogen-platinum system failed to detect it. In this case, however, manual injection of 15 c.c. of blood into a No. 5 catheter was necessarily slow. Typical curves obtained with the hydrogen-platinum system are shown in Fig. 9.

Detection of valvular regurgitation was readily accomplished. Blood or saline, previously exposed to hydrogen, was injected into a catheter which was placed in the chamber immediately downstream from the valve. Regurgitant blood was detected with the platinum-tipped catheter in the immediate upstream chamber. A typical curve is shown in Fig. 10.

Results of the experiments performed on the 5 dogs with subclavian-pulmonary arterial anastomoses are shown in Table I. In each case the hydrogen-platinum system clearly detected the shunt earlier than did the other two methods and before the appearance of the murmur. No attempt was made to quantitate the shunt by the

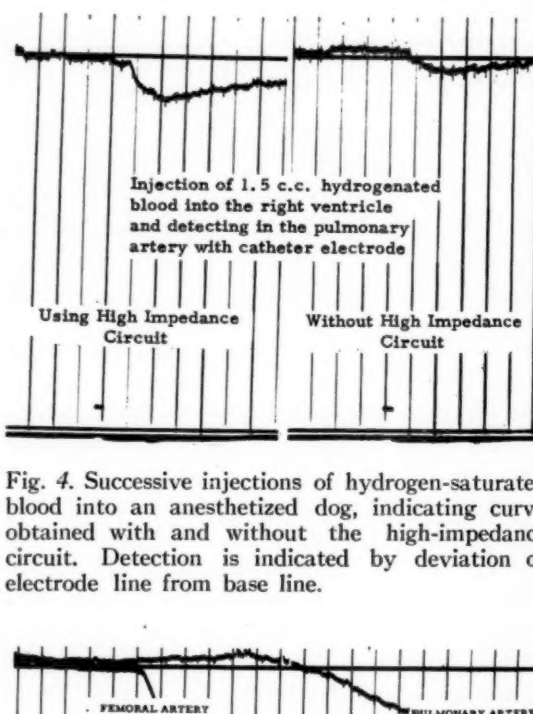

Fig. 4. Successive injections of hydrogen-saturated blood into an anesthetized dog, indicating curve obtained with and without the high-impedance circuit. Detection is indicated by deviation of electrode line from base line.

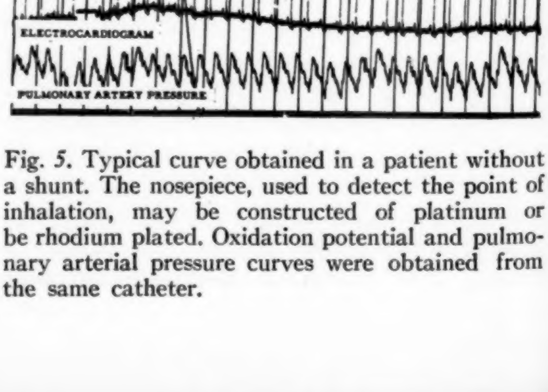

Fig. 5. Typical curve obtained in a patient without a shunt. The nosepiece, used to detect the point of inhalation, may be constructed of platinum or be rhodium plated. Oxidation potential and pulmonary arterial pressure curves were obtained from the same catheter.

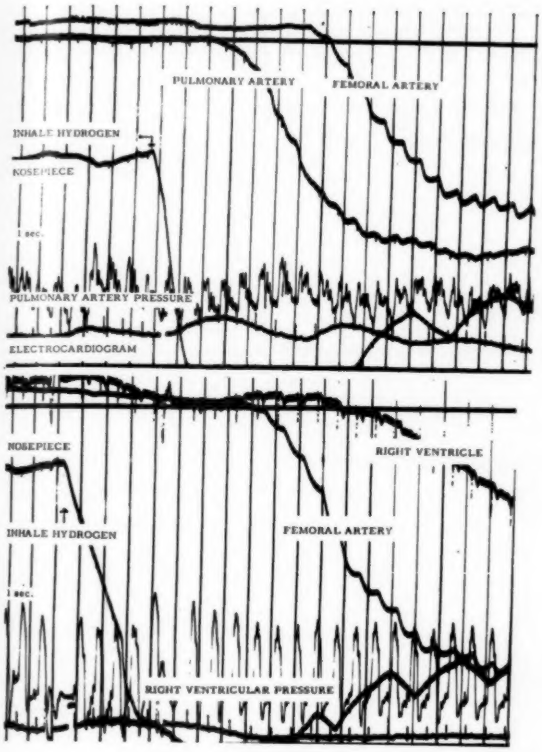

Fig. *6*. Curves obtained in a patient with patent ductus. The change in oxidation potential is 3 seconds after inhalation of hydrogen in the pulmonary artery, and 11.5 seconds in the right ventricle. A rhodium nosepiece was employed.

hydrogen-platinum system, but calculations were obtained after further deflation of the cuff permitted a great enough shunt to give positive results from the dye curves and the oxygen method (Table I).

The results of injection of hydrogenated blood into the external jugular vein and detection with an electrode catheter in the pulmonary artery indicate that as little as 2 c.c. injected at the rate of 13 c.c. per minute, with a cardiac output of 3 L. per minute, gave a clear signal (Fig. 11). Injection into the left ventricle of 3 c.c. of hydrogen-saturated blood at the rate of 43 c.c. per minute, with a cardiac output of 3 L. per minute, gave a clear signal from the electrode catheter in the femoral artery (Fig. 12).

Discussion

The hydrogen-platinum system has proved to be a reliable, simple, and accurate method for the detection and localization of small left-to-right shunts. The technique can be repeated as frequently as necessary at the catheterization table without the withdrawal of samples of blood for dye curves or the insertion of multiple catheters. Although this technique affords no known method for quantitation, removal of samples through the same catheter from the pulmonary artery and vena cava for analysis of oxygen content will allow estimation of the size of the shunt. The extreme sensitivity of the method, however, serves as a disadvantage in the presence of large shunts, when valvular regurgitation is likely to occur. Small amounts of hydrogen-labeled blood which appear early in the right heart are

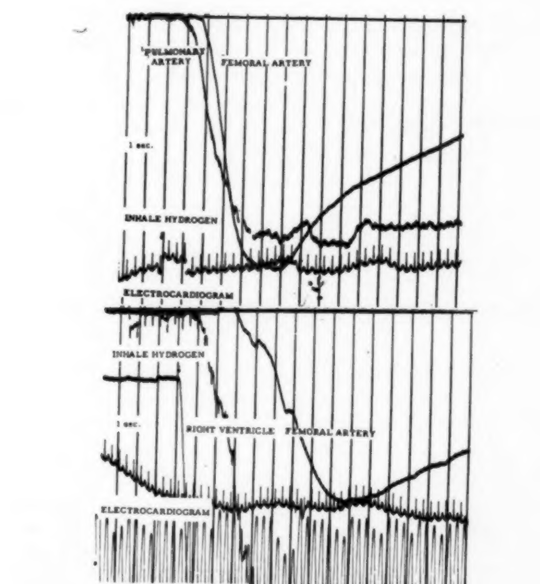

Fig. *7*. Curves obtained in a patient with ventricular septal defect with left-to-right shunt which is indicated by the late appearance of change in oxidation potential in the right atrium as compared to the right ventricle. A platinum electrode nosepiece was used for the signal of inhalation of hydrogen in recording the curve from the right ventricle, and interruption of the electrocardiogram was used for the other two curves.

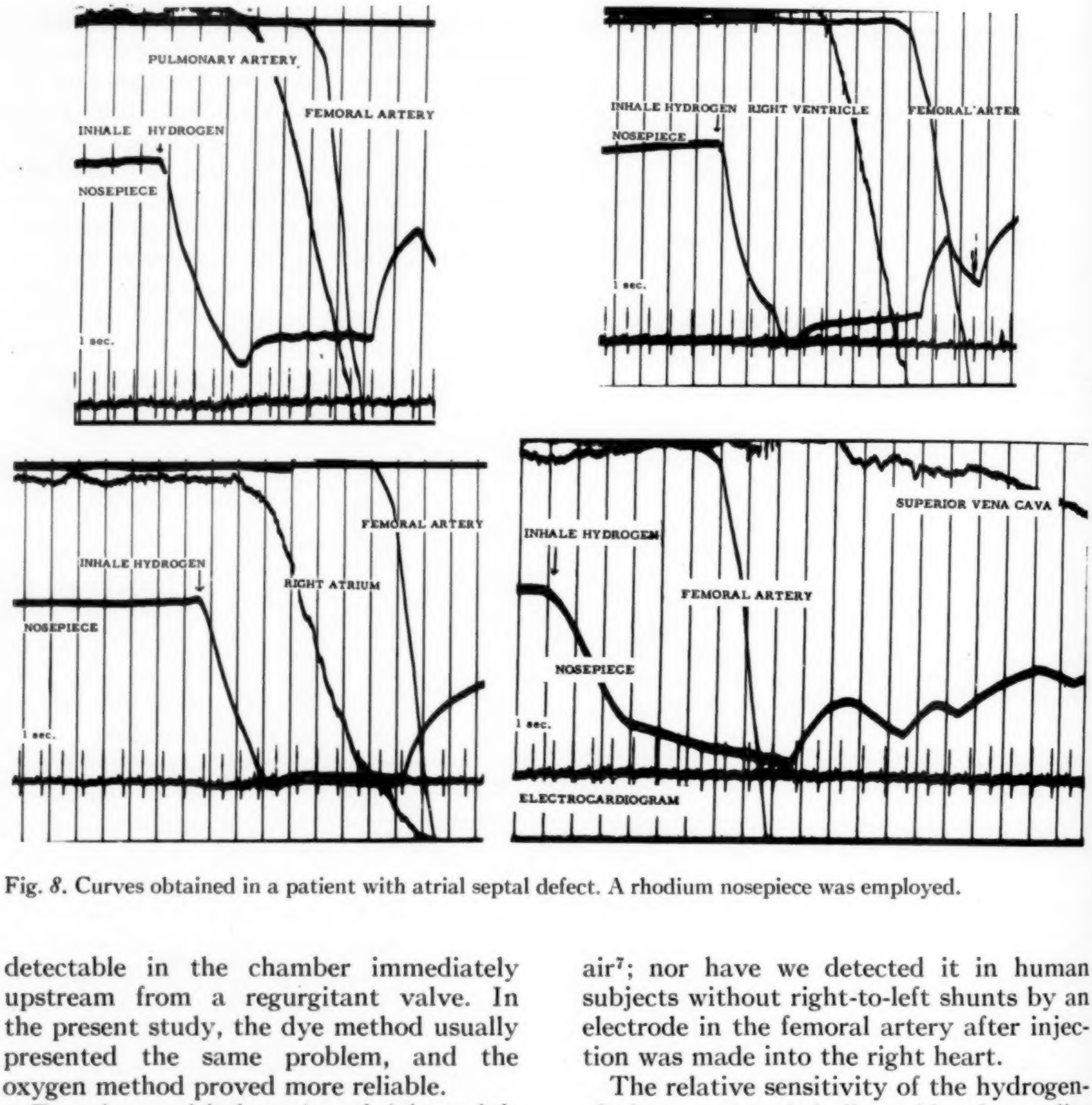

Fig. *8*. Curves obtained in a patient with atrial septal defect. A rhodium nosepiece was employed.

detectable in the chamber immediately upstream from a regurgitant valve. In the present study, the dye method usually presented the same problem, and the oxygen method proved more reliable.

Experience with detection of right-to-left shunts in this investigation is limited. It is apparent, however, that with larger shunts (greater than 20 per cent of the systemic venous return), localization is readily obtained with the hydrogen-platinum system. With smaller right-to-left shunts, more rapid injections should prove helpful. The low solubility of hydrogen in saline or blood is disadvantageous; the labeling is not so massive as that obtained in the lung after inhalation of hydrogen. The hydrogen-platinum system has the advantage of an unequivocal response. We have never detected hydrogen-labeled blood passing through the lungs of experimental animals by a platinum electrode in the left atrium or left ventricle, or in exhaled air[7]; nor have we detected it in human subjects without right-to-left shunts by an electrode in the femoral artery after injection was made into the right heart.

The relative sensitivity of the hydrogen-platinum system is indicated by the studies with subclavian-pulmonary arterial anastomoses. The oxygen method appeared to be more sensitive than previous experience in studies on congenital heart disease in this laboratory would suggest. However, in this study, the samples for analysis of oxygen content were removed from both catheters simultaneously, without their manipulation, in anesthetized animals. Additionally, the quantity of the shunt could not be accurately gauged by the stepwise deflation of the cuff about the subclavian artery.

The modification of the Clark electrical circuit offers the advantage of representing the oxidation potential more adequately, independent of the size of the platinum

electrode. Even with this more adequate registration of the natural logarithmic relationship of concentration to potential, quantitation of the hydrogen concentration, and, hence, the size of the shunt, is not readily accomplished.

Summary

A modification of the Clark hydrogen-platinum system is described, employing a high-impedance system, platinum-electrode catheters, and stylets for Cournand or Henry needles. Typical curves which illustrate the localization of left-to-right and right-to-left shunts are presented. Valvular regurgitation is readily detected. The advantages of the method are the simplicity and reliability of the detection

*Table I. Summary of results obtained by stepwise deflation of a Jacobson cuff placed about a subclavian artery which had been anastomosed to the pulmonary artery**

Cubic centimeters removed from cuff	H_2	*Dye*	O_2	*Murmur*
Dog No. 1:				
Occluded	0	0	0	0
0.10	+	0	0	0
0.15	+	0	0	0
0.20	+	0	0	Systolic component
0.25	+	+ .1 × PBF	+ .2 × PBF	Systolic and diastolic
Dog No. 2:				
0.05	+	0	0	0
0.10	+	0	0	Systolic component
0.15	+	+ .02 × PBF	+ .02 × PBF	Systolic component
Dog No. 3:				
0.05	0	0	0	0
0.10	+	0	0	0
0.15	+	0	0	0
0.20	+	+ .09 × PBF	+ .08 × PBF	0
Dog No. 4:				
0.05	0	0	0	0
0.10	+	0	0	0
0.15	+	+ .02 × PBF	0	0
0.20	+	+	0	0
All fluid removed	+	+ .15 × PBF	0	0
Dog No. 5:				
0.05	0	0	0	0
0.10	+	0	0	0
0.15	+	+ .4 × PBF	0	0
0.20	+	+	+ .5 × PBF	Systolic component

*Absence of a shunt is indicated by a zero. Evidence of a shunt is indicated by a plus sign. The numerals below the plus sign indicate the calculated shunt in terms of pulmonary blood flow.

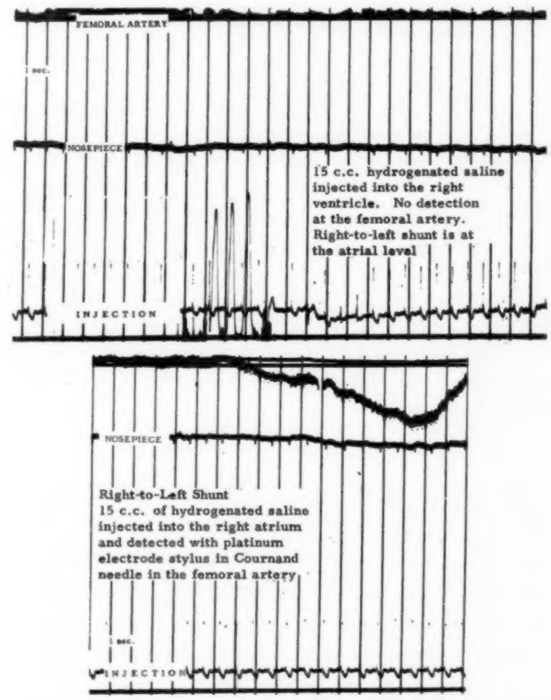

Fig. *9*. Curve obtained in a patient with pulmonary stenosis and right-to-left shunt at the atrial level. Hydrogenated saline gave a signal at the femoral artery, as indicated by its deviation from the base line only when injected at the atrial level or upstream, but failed when injected into the right ventricle or pulmonary artery. No change in oxidation potential was seen in the platinum nosepiece.

Fig. *10*. Curve showing detection of tricuspid regurgitation by means of a regular catheter for injection, and a platinum electrode catheter for detection. The signal is indicated by the deviation of the right atrial electrode catheter line from the base line.

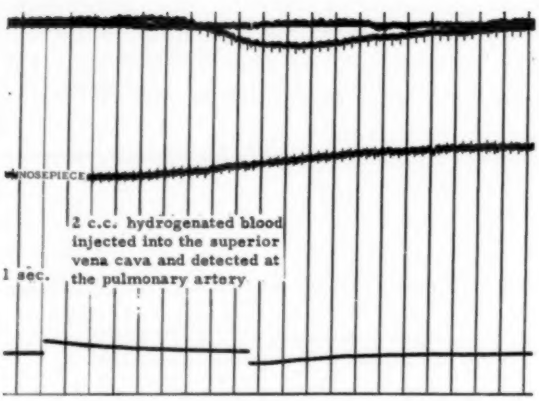

Fig. *11.* Curve showing detection of change in oxidation potential in pulmonary artery when 2 c.c. of hydrogenated blood was injected at rate of 13 c.c./min. into neck vein of a dog with cardiac output of 3 L./min.

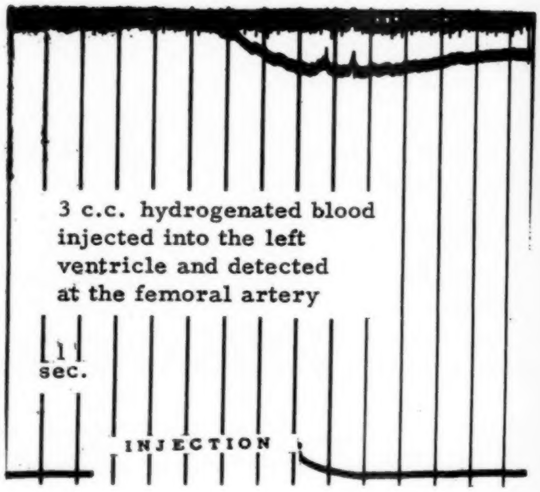

Fig. *12.* Curve showing detection of change in oxidation potential in the femoral artery of a dog when 3 c.c. of hydrogenated blood was injected into the left ventricle at a rate of 43 c.c./min. The cardiac output was 3 L./min.

and localization of small shunts by means of a single intracardiac catheter. The disadvantages of the method are its extreme sensitivity, which complicates evaluation of valvular regurgitation, and the lack of quantitation of the shunt volume.

Addendum

Recently, one of the authors (E.S.H.) devised a circuit that registers hydrogen as a linear function of its concentration at a platinum electrode in vitro and in simple in vivo experiments. By this method the aortic blood varies from 30 to 50 per cent saturated with hydrogen with various inhalations of 100 per cent hydrogen.

We express appreciation to Mr. Dewey Pailet, jeweler, and Mr. H. H. Schmidt, jeweler's manufacturer, for assistance with royal metals, and to Superior Tubing Co., Norristown, Pa., for the stainless steel needle tubing.

REFERENCES

1. Morrow, A. G., Sanders, R. J., and Braunwald, E.: The nitrous oxide test: An improved method for the detection of left-to-right shunts, Circulation **17**:2, 1958.
2. Sanders, R. J.: Use of radioactive gas (Kr^{85}) in diagnosis of cardiac shunts, Proc. Soc. Exper. Biol. & Med. **97**:1, 1958.
3. Case, R. B., Hurley, H. W., Keating, R. P., Keating, P., Sachs, H. L., and Loeffler, E. E.: Detection of circulatory shunts by use of a radioactive gas, Proc. Soc. Exper. Biol. & Med. **97**:4, 1958.
4. Clark, L., Jr., and Bargeron, L. M., Jr.: Detection and direct recording of left-to-right shunts with the hydrogen electrode catheter, Surgery **46**:4, 1959.
5. Swan, H. J. C., Zapata-Diaz, J., and Wood, E. H.: Dye-dilution curves in cyanotic congenital heart disease, Circulation **8**:70, 1953.
6. Hyman, A. L., Levy, L., II, Bagnetto, R., and Ordway, N.: Application of newer diagnostic methods in congenital heart disease, New Orleans M. & S. J. **103**:1, 1950.
7. Hyman, A. L., Hyman, E. S., Quiroz, A. C., and Gantt, J. R.: Comparison of the platinum-rhodium-hydrogen electrode and oxygen methods in detecting shunts, S. Forum **11**:1960. (In press.)

Experimental and laboratory reports

Analysis of heart motion with ultrasonic Doppler method and its clinical application

*Tsuneo Yoshida, M.D.**
*Masayoshi Mori, M.D.**
*Yasuharu Nimura, M.D.**
*Gen-ichi Hikita, M.D.**
*Shinpachi Takagishi, M.D.**
*Katsumi Nakanishi, M.D.**
*Shigeo Satomura, M.S.***
Osaka, Japan

Ultrasound has been used in industry to detect flaws in metal and to sound the depth of the sea; a good transmittance and sharp direction of ultrasound in a given substance can attest such utilization. Quite naturally, too, ultrasound has been used to study the inner aspects of the human body. It was first employed in detecting tumors and gallstones,[1-7] and has also been applied to the heart, by Keidel,[8] Edler and Hertz,[9-11] Wild,[12] and others.

In the present study the ultrasonic Doppler method was adopted. It features a device to represent the movements of the target to be examined, and enables one to detect the time in which movements of the valves occur.

Method

A. Principle.

1. TRANSMITTANCE, DIRECTION, AND REFLECTION IN THE BODY OF THE ULTRASOUND. Ultrasound is a sonic wave with a frequency above the audible range (16 c.p.s.-16,000 c.p.s. on an average). The propagation of ultrasound follows the Huygens principle, as in the case of an audible sound. When an ultrasound which has a wave length λ is sent in one direction from a circular plane source having diameter d, 90 per cent of the energy of the ultrasound is included in solid angle θ, which is determined by the following formula[13,14]:

$$\sin \theta = 1.22\ \lambda/d$$

where θ is small, since λ of the ultrasound is small, i.e., the energy of the ultrasound is sent mostly in one direction, with little divergence. Thus it is understood that the ultrasound possesses a sharp direction. The ultrasound has a straight propagation into the living body, as does x-ray. It can be used in examining those targets in the path of its transmission.

When the ultrasound is transmitted into the living body from its surface, a part of the transmission is reflected from the boundary between two living tissues which possess different sound impedances.

Received for publication Feb. 16, 1960.
*From the First Department of Medicine, Osaka University Medical School, Osaka, Japan.
**From the Institute of Industrial and Scientific Research, Osaka University, Osaka, Japan.

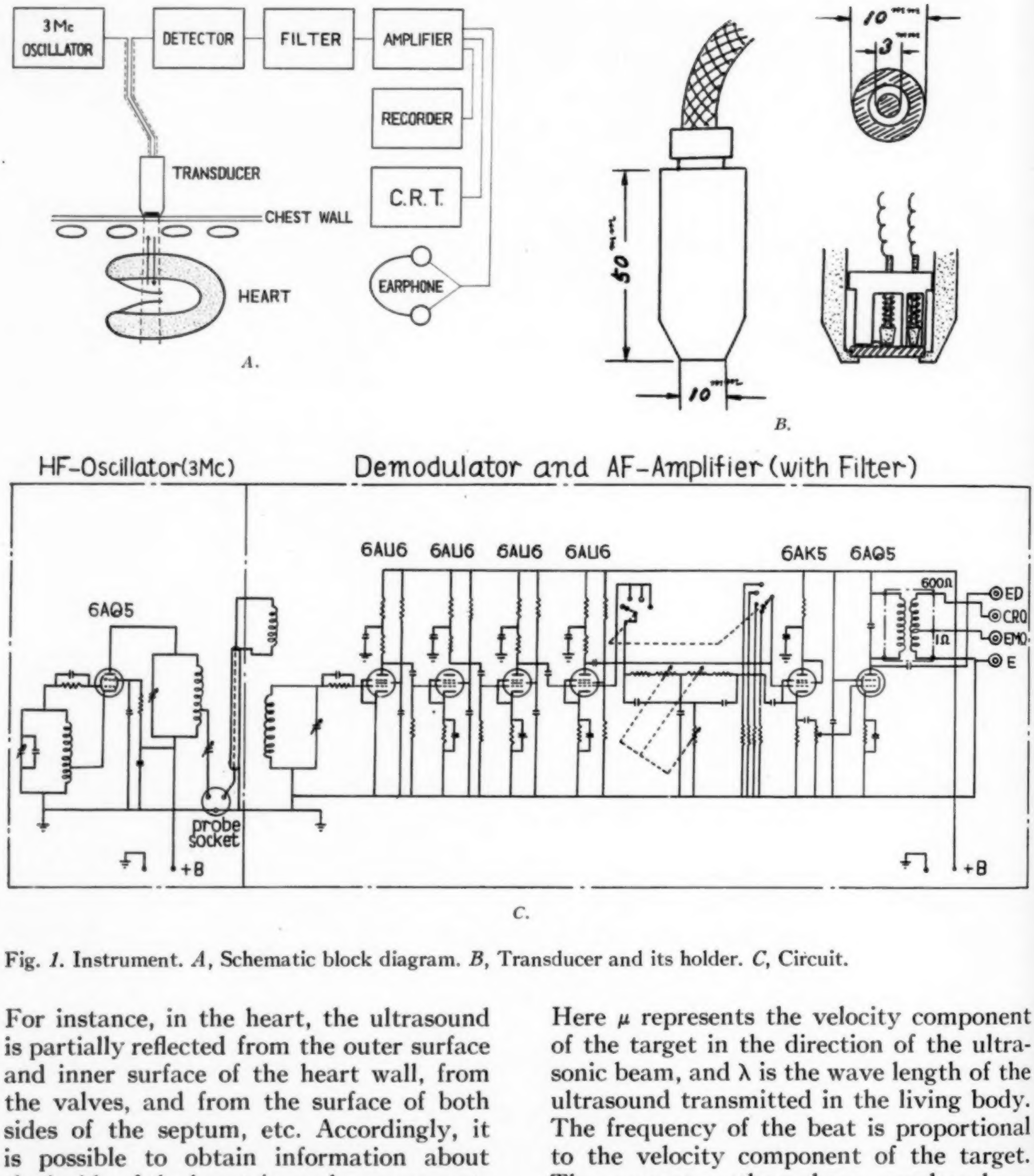

Fig. *1.* Instrument. *A*, Schematic block diagram. *B*, Transducer and its holder. *C*, Circuit.

For instance, in the heart, the ultrasound is partially reflected from the outer surface and inner surface of the heart wall, from the valves, and from the surface of both sides of the septum, etc. Accordingly, it is possible to obtain information about the inside of the heart (e.g., the movements of the valves) which would be denied to other methods, such as x-ray.

2. PRINCIPLE OF THE ULTRASONIC DOPPLER METHOD. When the continuous beam is transmitted from the chest wall to the heart, and is reflected from the heart wall and valves, it undergoes Doppler effect subject to the movements of the heart.[15,16] When this reflected wave is detected together with the direct wave, a beat appears, the frequency of which is (f_d)

$$f_d = 2\ \mu/\lambda.$$

Here μ represents the velocity component of the target in the direction of the ultrasonic beam, and λ is the wave length of the ultrasound transmitted in the living body. The frequency of the beat is proportional to the velocity component of the target. The present authors have employed an amplifier for observance of this beat in an attempt to get information about the heart wall, valves, etc.[17] When the target is kept still, i.e., strictly speaking, when the velocity of the target does not possess a component in the same direction as the ultrasonic beam, no beat occurs. Hence, this method is considered to be closely related with the movements of the target examined.

B. Instrument. Fig. 1 describes the schema of the apparatus[15] used. The high-

frequency oscillator employed was of 1-2 watts, the frequency being 3 megacycles per second. A disc of barium titanate, 1 cm. in diameter, was used as the electrosonic transducer. The disc was divided into two parts, being a concentric circle. The inner and outer parts were used for sending and detection, respectively (Fig. 1,*B*). In the area for detection the direct wave as well as the reflected waves were detected electrically or mechanically: a beat develops between these two waves.

The calculated value of the power of the ultrasound was about 20-50 milliwatts per square centimeter. Cavitation which causes influential physiologic effects on the living tissue develops mostly at over 300 milliwatts per square centimeter. Therefore, in the present study, the intensity of ultrasound employed for a few minutes seems to be free from any untoward side effects. The aforesaid θ was about 4 degrees. An ordinary type of pentode grid demodulator was used as a detector. The amplification of the low-frequency amplifier was 60-80 decibels. As the filter, a low-pass (cut-off frequency 200 c.p.s.) filter and a band-pass filter of 500-1,000 c.p.s. were employed.

The Doppler signal was recorded by means of an electromagnetic oscillograph under the control, with an earphone and/or a Braun tube. The paper speed was 20-30 cm. per second. We usually recorded the Doppler signal simultaneously with the ECG and PCG and made comparative study of these. Fig. 1,*C* shows the diagram of the apparatus employed.

Results and discussion

Part I. The kinds of Doppler signal due to heart movements.

1. THE KINDS OF DOPPLER SIGNAL DUE TO HUMAN HEART. When this method was applied to a human body, a transducer was closely attached to the precordial area. Here, fluid paraffin was employed for the removal of the air between the skin and the transducer so as to give a good contact. The Doppler signal can be obtained in any area in which the heart is attached to the chest wall. But, when transmission to the target is carried out through the lung, the ultrasound is absorbed by the air in the lung, and it is difficult to obtain the Doppler signal with the intensity of ultrasound used in the present study. Occasionally, it is difficult to obtain the recording in an athletic human body which has a short and wide thorax. Moreover, ultrasound does not transmit through bone tissues.

The Doppler signal thus obtained was classified into the following two kinds in terms of frequency[18,19]: (a) low-frequency signal of less than 500 c.p.s., mostly 100-200 c.p.s., and (b) high-frequency signal of about 1,000 c.p.s. In the present study,

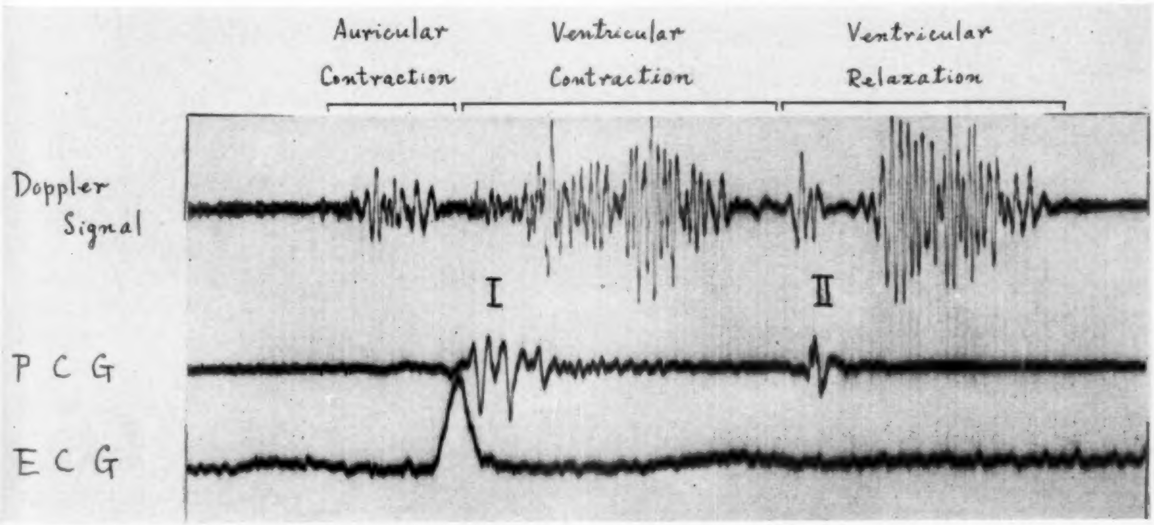

Fig. 2. Ultrasonic Doppler signal of low frequency (in the fourth left intercostal space at the parasternal line) related to the movement of the heart wall.

a filter was generally used to record these two signals separately.

2. THE LOW-FREQUENCY SIGNAL. The low-frequency signal obtained in healthy subjects is shown in Fig. 2. When compared with the ECG and the PCG which were recorded concurrently, this signal begins to appear within almost 0.04-0.09 second

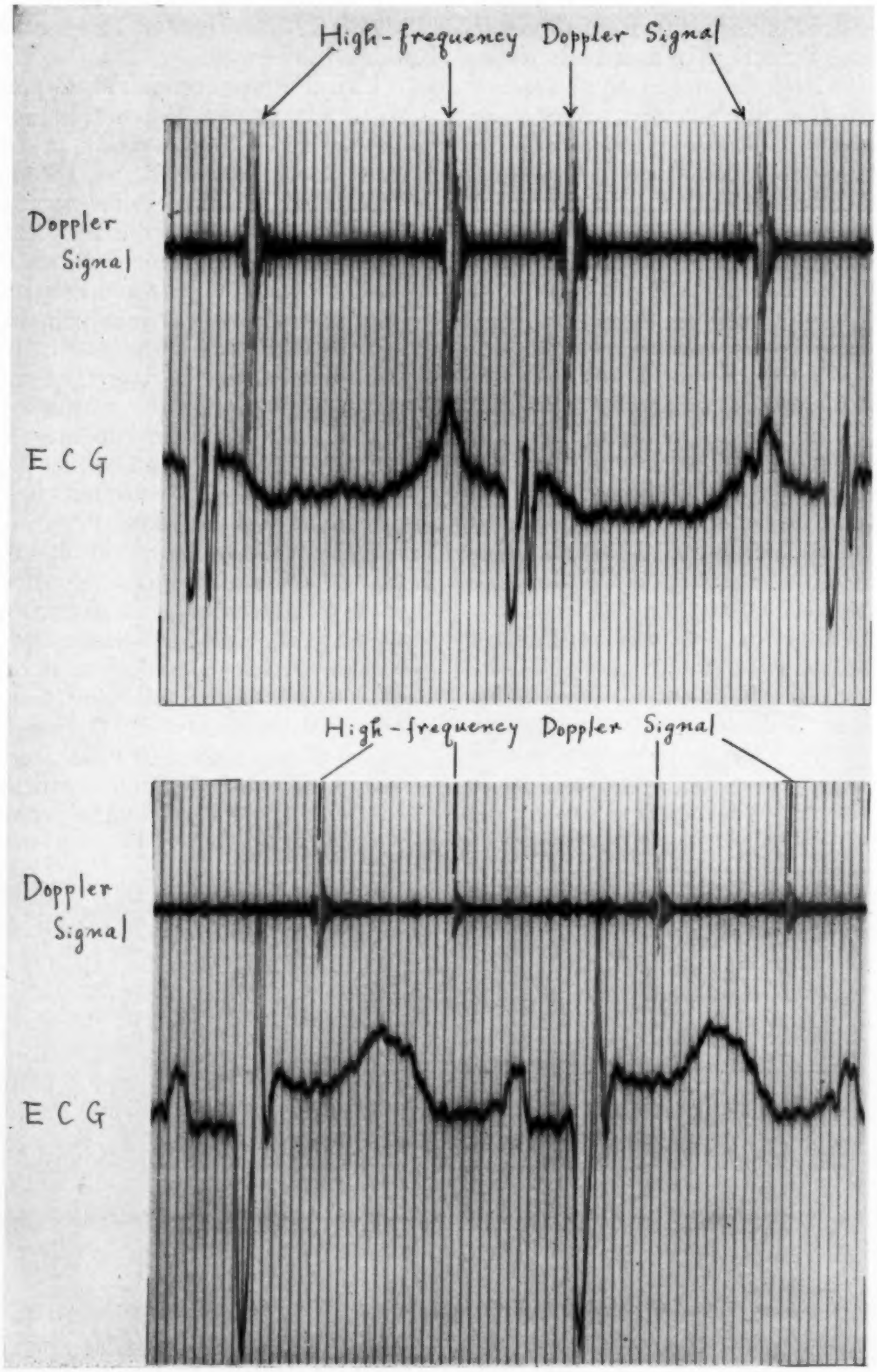

Fig. 3. High-frequency Doppler signal related to the movement of the valve (exposed dog heart). *Top:* Tricuspid valve. *Bottom:* Pulmonic valve.

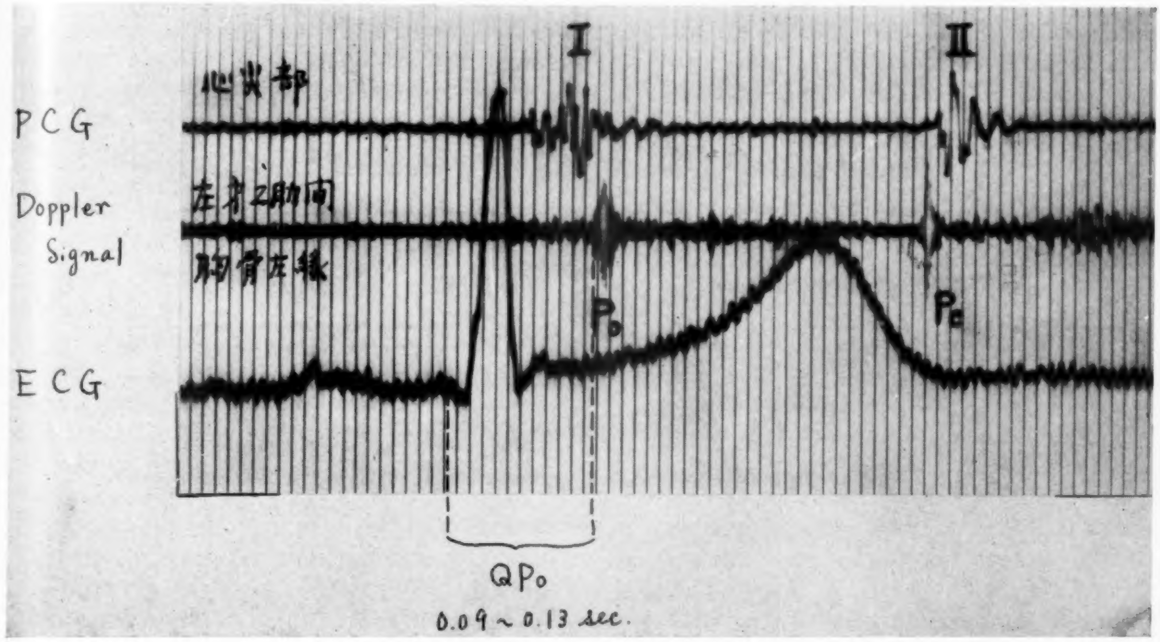

Fig. 4. Ultrasonic Doppler signal of high frequency related to the pulmonic valve. *Po:* Opening. *Pc:* Closing. The end of *Pc* coincides with the beginning of the second heart sound. (S. T., a 30-year-old healthy man.)

after the beginning of the QRS, nearly at the same time as the beginning of the first heart sound.

The first half of the low-frequency signal lasts almost until the summit of the T. The latter half begins almost at the same time as the second heart sound, and lasts for about 0.3 second. It is reasonable to consider that this low-frequency signal is related to the movements of the heart wall, and that its first and latter halves are due to the movement in systole and diastole, respectively. The site for low-frequency signal in the present study was generally represented by the fourth intercostal space on the left parasternal line.

Besides the aforementioned low-frequency signal, a low-frequency signal appears at the time corresponding to the P-Q (Fig. 2). This low-frequency signal begins 0.08-0.13 second after the beginning of the P (mostly in 0.10-0.11 second) and lasts for 0.07-0.12 second. The time of the beginning and the duration of this low-frequency signal are similar to the time of beginning and the duration of the auricular sound.[19,20] This signal is considered to indicate the movements of the heart wall which accompany an auricular contraction.

3. THE HIGH-FREQUENCY SIGNAL. The high-frequency signal appears subsequent to the QRS as well as nearly at the end of the T, and it lasts for a short time (Figs. 4 and 6). With regard to its frequency, the target is understood to move with a speed several times faster than that of the target of the aforesaid low-frequency signal. Considering this high speed and the time of appearance, it is understood that the target examined must be a valve (tendon, papillary muscles, etc., may also be referable). The finding that the time of appearance of the high-frequency signal is slightly different in the basal area from that in the apical area can be reasonably interpreted in accordance with the difference of the time of the movements in the semilunar valve from that in the atrioventricular valve.

4. EXPERIMENT IN EXPOSED DOG HEART. An attempt was made to confirm that the high-frequency signal is related to valvular movements. A transducer was applied on the exposed surface of the dog heart in order to ascertain where the high-frequency signal could be obtained,[21] and we found that the signal could be obtained in the vicinity of (a) the tricuspid valve, (b) the mitral valve, and (c) the pulmonic valve, when the ultrasonic beam was sent toward these valves.

In the vicinity of the tricuspid valve the

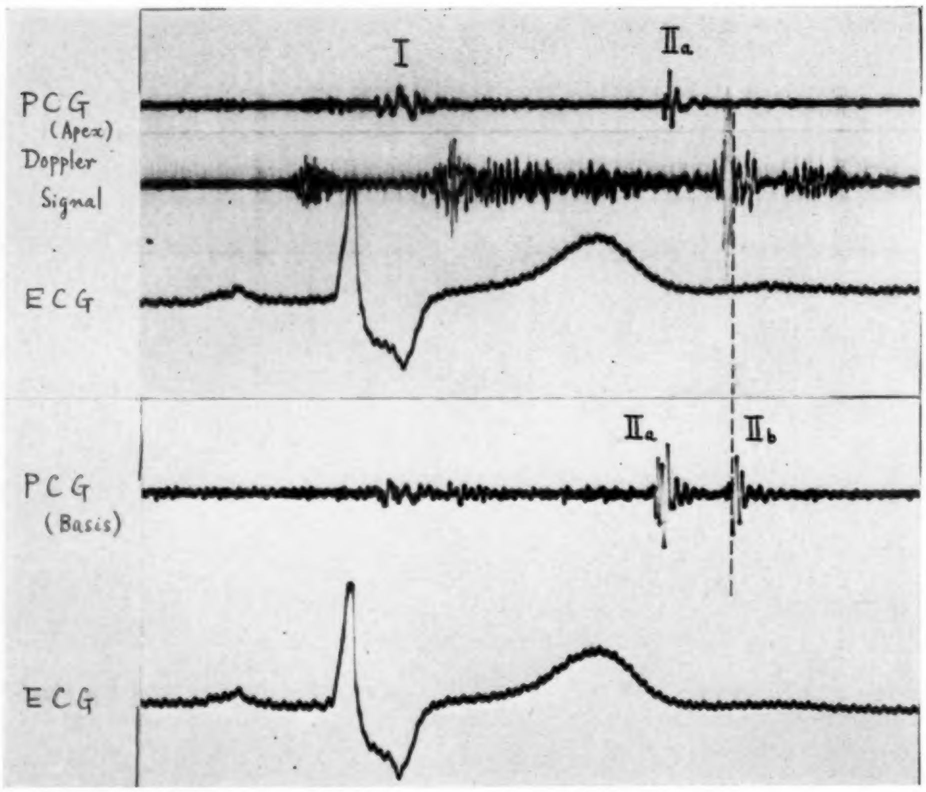

Fig. 5. Delayed closing of the pulmonic valve in RBBB. Second basal sound is reduplicated. Its earlier component *IIa* is interpreted as being due to the aortic valve; its later component *IIb* is due to the pulmonic valve. The latter does not appear in the apical region. Doppler signal Pc has been obtained in the second intercostal space at the left sternal edge. Its end coincides, as expected, with the beginning of IIb. (H. A., a 30-year-old man.)

high-frequency signal begins 0.04 to 0.05 second after the beginning of the QRS and 0.05 second after the end of the T (Fig. 3, *top*). The time of appearance is about the same in the vicinity of the mitral valve. In the vicinity of the pulmonic valve the high-frequency signal appears 0.09 second after the beginning of the QRS and nearly at the end of the T (Fig. 3, *bottom*). Thus, in regard to early systole, the high-frequency signal obtained in the vicinity of the tricuspid valve appears 0.04 second earlier than that in the vicinity of the pulmonic valve. On the contrary, in regard to nearly the end of the T, the high-frequency signal obtained in the vicinity of the pulmonic valve appears 0.05 second earlier than that in the vicinity of the tricuspid valve. When the site and time for the development are considered, such a high-frequency signal seems to be related to the movements of the related valves, probably inclusive of chordae tendineae and papillary muscles, and to denote the time of movements. It is understood that the time intervals between the signal of the pulmonic valve and that of the tricuspid valve in early systole and at nearly the end of the T signify the duration of isometric contraction and the duration of isometric relaxation, respectively.

In so far as the time of development and the frequency are concerned, the high Doppler signals obtained on the human chest wall correspond to those of the aforesaid dog. Therefore, this seems to confirm that the high-frequency signal from a human being indicates the time of valvular movements.

Part II. The high-frequency Doppler signal due to valvular movements in a human being and its clinical application.

1. THE HIGH-FREQUENCY DOPPLER SIGNAL DUE TO VALVULAR MOVEMENTS. The high-frequency Doppler signal in a human being[19,20] which is considered to be due to

the movements of the semilunar valves is most clearly recorded exclusively with the transducer on the left sternal edge in the third intercostal space, sometimes in the second or fourth intercostal spaces (Fig. 4). On the basis of the findings in cases of bundle branch block or reduplicated basal second sound, as mentioned later on, it is concluded that the Doppler signal due to the aortic valve is obtained on the left sternal edge in the third or fourth intercostal space, and the Doppler signal due to the pulmonic valve is obtained on the left sternal edge in the third or second intercostal space. A semilunar valve is so small a target that it needs a limited site of the transducer and a limited direction of the ultransonic beam.

The Doppler signal due to the opening of a semilunar valve in a healthy human being appears 0.09-0.14 second after the beginning of the QRS; the signal due to the closing of a semilunar valve appears just before the second heart sound, and its termination coincides with the beginning of the second heart sound (Figs. 4 and 5).

According to this finding, the second heart sound develops almost simultaneously with the completion of the closing of a valve; that is, the second heart sound seems not to be caused by the movements of the valves themselves, but by the tens on or vibration of the related valves and their adjacent tissues due to impulses which develop directly after the closing.

Strictly speaking, it is frequently difficult to define in a human being whether the Doppler signal due to a semilunar valve is caused by the pulmonic valve or by the aortic valve. Mostly, both valves seem to move simultaneously. But in some cases the two signals due to these valves can be differentiated as to time and site. Then the opening of the aortic valve (Ao) begins 0.09-0.14 second (average 0.107 second: 7 cases) after the beginning of the QRS, and the opening of the pulmonic valve (Po) begins 0.09-0.13 second (0.106 second: 25 cases) after (Table I). But in cases in which both signals are recorded, Po precedes Ao by 0.02 second or less. Moreover, the signal due to either of these valves is obviously differentiated in cases with bundle branch block and cases with a reduplicated or split second heart sound. As soon as the signal for the closing of the aortic valve or pulmonic valve (Ac or Pc, respectively) terminates, the respective component of the second heart sound begins (Fig. 5).

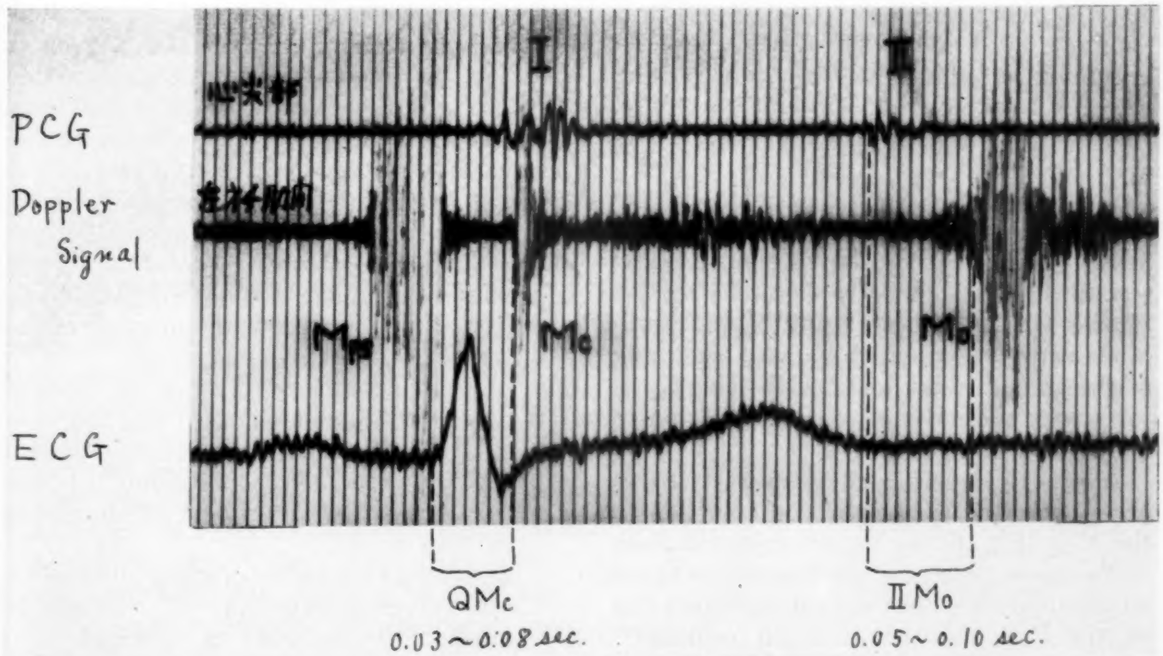

Fig. 6. Ultrasonic Doppler signal of high frequency interpreted to be related to the mitral valve. *Mc:* Closing. *Mo:* Opening. (S. N., a 35-year-old man.)

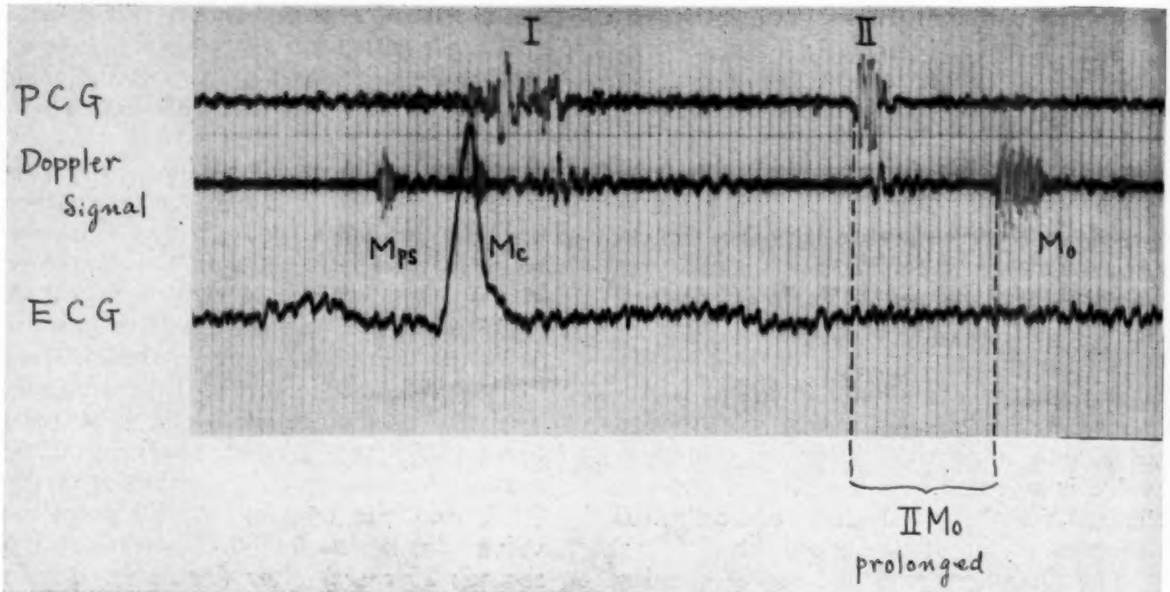

Fig. 7. Delayed opening of the mitral valve in myocardial change. (T. S., a 52-year-old woman with hypertension.)

The Doppler signals which seem to be related to the atrioventricular valve, especially those due to the mitral valve, are most likely to be detected on the left parasternal line in the fourth intercostal space.

Of these signals, the signal due to the closing of the mitral valve (Mc) in a healthy human being begins 0.03-0.08 second (average 0.054 second: 76 cases) after the beginning of the QRS (Table II); the interval between the Mc and the QRS varies with different pathologic conditions (Fig. 6).

The signal due to the opening of the mitral valve (Mo) in a healthy human being begins 0.05-0.10 second (0.069 second: 81 cases), mostly 0.06-0.08 second (Table III) after the closing of the semilunar valve is completed, i.e., the beginning of the second heart sound (II). The signal for either the closing or opening requires about 0.02-0.04 second.

Another high-frequency signal (Mps) appears at the time which corresponds to the P-Q (Fig. 6). It begins approximately at the same time as a low-frequency signal which appears at the interval corresponding to the P-Q and the auricular sound,[19,20] i.e., 0.10 to 0.13 second after the beginning of the P. In cases in which there is complete atrioventricular block, Mps accompanies the P, independently of the QRS. It does not appear in cases in which there is auricular fibrillation. When these findings are considered, it is assumed that Mps is caused by valvular movements which are due to an inflow of the blood into the ventricle at the time of auricular contraction.

The Doppler signal which is due to the tricuspid valve is obtained on the left lower sternal edge. That signal is frequently difficult to differentiate from the signal due to the mitral valve, as to time and site. Both valves seem to open almost simultaneously. But in some cases a signal (Tc) which can be defined as obviously being due to the tricuspid valve occurs 0.04-0.05 second (average 0.043 second: 9 cases) after the beginning of the QRS (Table II). At that time it precedes the opening of the mitral valve by 0.01-0.02 second.

In cases in which there is a great interval between the time of the right and left ventricular contractions, e.g., bundle branch block, the respective signals due to these two valves can obviously be differentiated from each other.

Thus, the time of the opening and closing of the valves, if detected, will lead one to determine the duration of isometric contraction, isometric relaxation, etc. Of course, it is possible to measure the isometric relaxation on the left side and right

Table I. *Time of opening of semilunar valves*

Second	*QAo (Number of cases)*	*QPo (Number of cases)*
0.09	2	5
0.10	2	7
0.11	1	8
0.12	1	4
0.13	0	1
0.14	1	0
	7	25

Table II. *Time of closing of atrioventricular valves*

Second	*QMc (Number of cases)*	*QTc (Number of cases)*
0.03	1	0
0.04	14	6
0.05	28	3
0.06	20	0
0.07	10	0
0.08	3	0
	76	9

Table III. *Duration of isometric relaxation (IIMo)*

Second	*IIMo (Number of cases)*
0.05	10
0.06	23
0.07	28
0.08	9
0.09	9
0.10	2
	81

side separately under the conditions wherein the opening and closing of the pulmonic valve (Po, Pc) and of the tricuspid valve (To, Tc) can be differentiated from the opening and closing of the aortic valve (Ao, Ac) and the mitral valve (Mo, Mc). Here it must be admitted that since the end of the closing of the semilunar valves coincides with the beginning of the second heart sound, the duration from the beginning of the second heart sound (II) to the beginning of Mo (To) is used as the duration of isometric relaxation instead of the duration from the beginning of the closing of the semilunar valves to the beginning of Mo, for the convenience of recording in the following description.

The duration of isometric contraction in healthy persons is 0.03-0.08 second. The duration of isometric relaxation (IIMo) in most cases is 0.06 to 0.08 second (Table III); cases of bradycardia show, mostly, a trend of slight prolongation of isometric relaxation.

2. FINDINGS IN PATHOLOGIC CASES. The time of valvular movements detected by the present method varies according to different pathologic conditions; above all, the time of opening of the mitral valve (Mo) is especially variable, and results in marked changes in the duration of isometric relaxation. The findings so far obtained of the time of valvular movements are presented below.

a. Myocardial changes (coronary sclerosis and hypertensive heart disease): Cases in which there are ST-T changes in

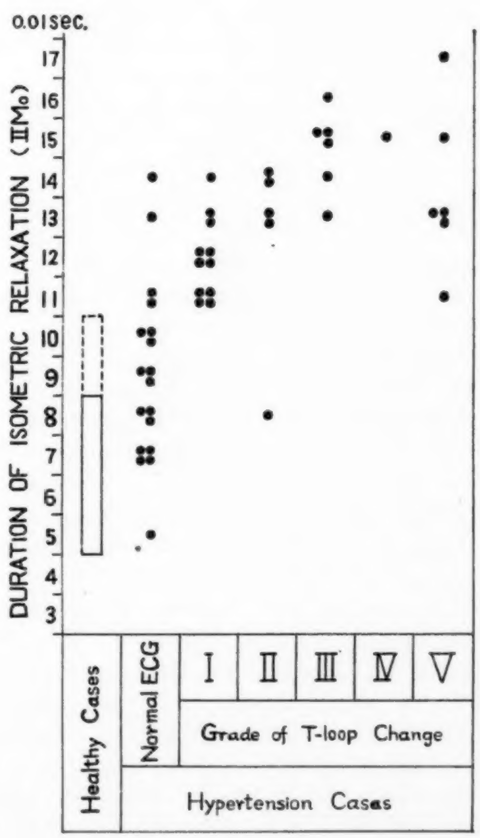

Fig. 8. Relationship between duration of isometric relaxation and grade of T-loop change in cases of hypertension and left ventricular strain pattern.

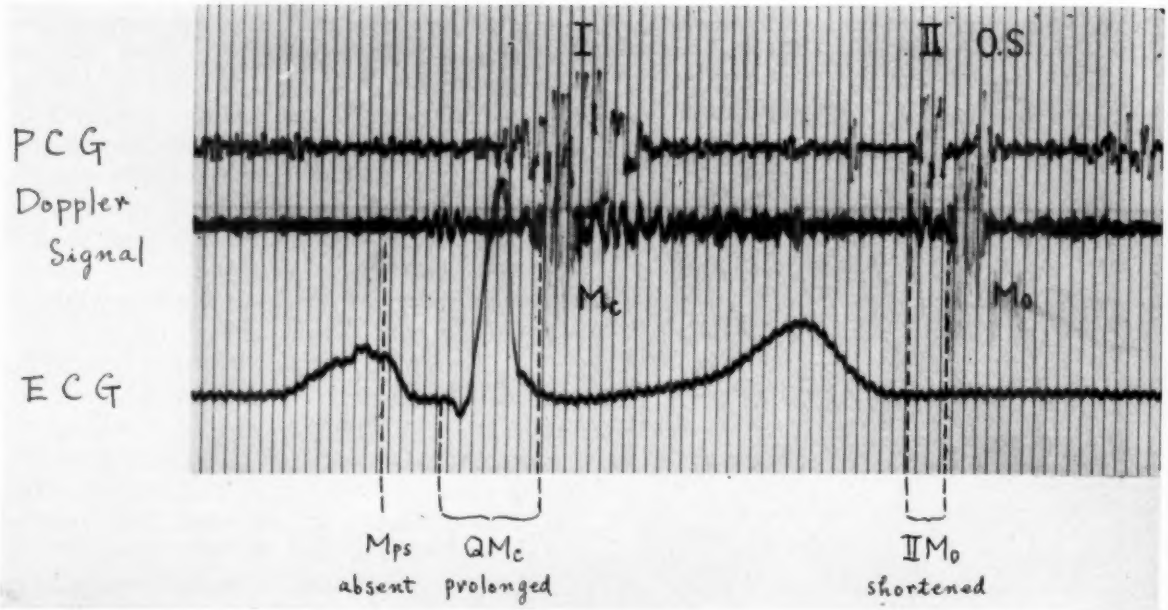

Fig. 9. Movements of the mitral valve in mitral stenosis. *Mps* is absent. *Mc* is slightly delayed; *IIMo* is shortened. The opening snap begins while *Mo* develops. (S. D., a 38-year-old man with mitral stenosis.)

the left precordial leads (with a few exceptional cases) show a markedly delayed opening of the mitral valve over the end of the T (Fig. 7). The isometric relaxation is over 0.10 second, mostly 0.12-0.14 second, and occasionally reaches 0.18 second. The mechanism of such delay has not been clarified. But the delay suggests that a certain factor, or factors, disturbs a smooth shift of the myocardium from mechanical systole to mechanical diastole. Electrocardiographically, a delayed repolarization of the myocardium, especially of the outer layer of the myocardium, may be interpreted as playing a great role in the mechanism of ST-T changes. The existence of a relationship between an electrical delay and a mechanical delay is suggested, leaving a problem to be pursued in the future.

b. Hypertension: Generally, cases of hypertension show a delay in Mo. But there is no close relationship between the grade of hypertension and the grade of delay. Cases in which there is a normal ECG show mostly a slighter grade of delay than the aforesaid cases in which there are ST-T changes. The severity of the left ventricular strain pattern has been classified by us on a vectorcardiographic basis into five grades.[22,23] According to this classification, it seems that the severer the grade of ST-T changes, the longer the duration of isometric relaxation (Fig. 8). However, some cases in which there is a normal ECG show also a delay occasionally. They even show marked changes. This seems to afford promise of an early detection of myocardial changes.

c. Mitral valvular disease: In cases of mitral stenosis and mitral stenosis and regurgitation without auricular fibrillation,[24] generally no Mps develops in the presence of the P (Fig. 9). The disappearance of the Mps was observed in all of 29 cases of stenosis, and in all but 3 of 18 cases of stenosis and regurgitation. This result seems to shed a bright light on the facilitation of diagnosis. The mechanism of the disappearance of the Mps has been left obscure, but a possible interpretation is that the movements of the mitral valve may be limited by the hardness of the valve.

Other representative findings in mitral valvular disease are a delayed closing of the mitral valve and an early development of the opening of the mitral valve, i.e., a trend of prolongation of QMc and a shortening of IIMo (Fig. 9).

The prolongation of QMc is comparable to the PCG finding in which the first heart

sound develops late in cases of mitral valvular disease.[25-28] Its mechanism may be referable to an insufficient ventricular filling, an elevated left auricular pressure, and a delay in elevation of the left ventricular pressure due to a regurgitation.

Elevation of the left auricular pressure is suggested as a factor which induces early opening of the mitral valve. In this study an attempt was made to find a relationship between IIMo-duration and the ECG abnormalities (Table IV). In cases of mitral stenosis, those in which right ventricular hypertrophy, or a trend toward it, is shown on the ECG reveal a more marked shortening of IIMo than do those cases in which QRS is normal on the ECG. Both these two abnormal findings seem related to a marked elevation of left auricular pressure. On the other hand, cases of mitral stenosis and regurgitation show a trend of marked shortening of IIMo even in the presence of normal findings on the ECG. This may be attributable to a specific elevation of left auricular pressure at the final stage of systole due to regurgitation, or attributable to an apparently normal ECG because of a mutual cancellation in the ECG of the influence of left and right ventricular hypertrophy.

A study of the opening of the mitral valve made in comparison with the opening snap reveals that the latter seems to begin in correspondence with the middle of the duration of the former (Mo) (Fig. 9).

During the present study there was a IIMo of 0.04 second in one case, and after commissurotomy it was 0.06 second.

A trend in the shortening of IIMo is also observed in cases of congestive heart failure of other etiology.

Here it must be added that in a case of mitral stenosis with right ventricular hypertrophy a delay in the opening of the tricuspid valve, i.e., a prolongation of the IITo to 0.10 second, was seen.

Cases of auricular fibrillation tend to demonstrate the effects of auricular fibrillation[21,24] markedly. QMc is related to the preceding R-R. A general trend is that the shorter the latter, the longer the QMc; that is, the longer the preceding R-R, the more delayed is the closing of the mitral valve. Eliakim and others[29] stated the same opinion on the basis of heart catheterization. IIMo is not so much shortened in cases of auricular fibrillation. Its relationship with the preceding R-R is not clearly detected. However, it is likely that a markedly short preceding R-R is accompanied by a more or less short IIMo.

d. Kidney diseases: Cases of nephritis show a delayed opening of the mitral valve and a prolongation of isometric relaxation. Such abnormalities are generally marked in cases of impaired renal

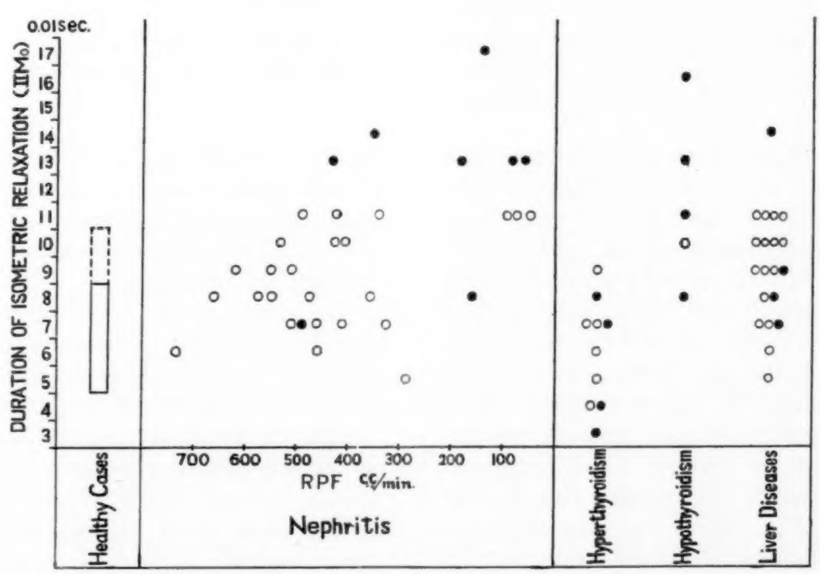

Fig. *10*. Duration of isometric relaxation under various conditions. The white circles indicate cases in which the ECG was normal, and the black circles indicate cases in which myocardial change was shown in the ECG.

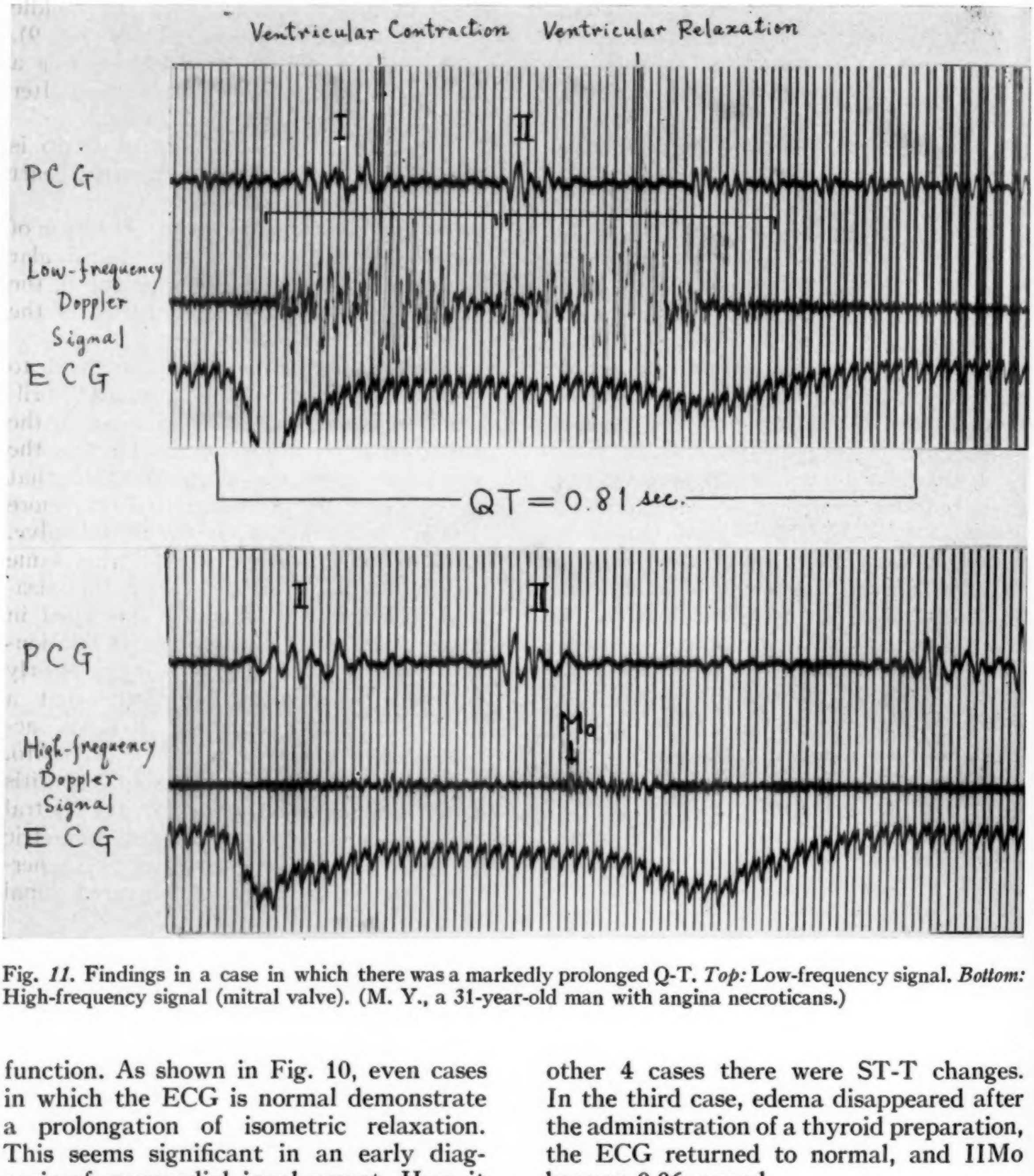

Fig. 11. **Findings in a case in which there was a markedly prolonged Q-T.** ***Top:*** **Low-frequency signal.** ***Bottom:*** **High-frequency signal (mitral valve). (M. Y., a 31-year-old man with angina necroticans.)**

function. As shown in Fig. 10, even cases in which the ECG is normal demonstrate a prolongation of isometric relaxation. This seems significant in an early diagnosis of myocardial involvement. Here it must be admitted that such prolongation is due to an early development of the second heart sound in a few cases.

e. Dysfunction of thyroid gland: Ten cases of hyperthyroidism without myocardial change in the ECG showed no marked changes in the opening time of the mitral valve (Fig. 10). Five cases of hypothyroidism showed a IIMo duration of 0.16, 0.13, 0.11, 0.10, and 0.08 second (Fig. 10); the fourth case (0.10 second) showed a Q-T prolongation, and in the other 4 cases there were ST-T changes. In the third case, edema disappeared after the administration of a thyroid preparation, the ECG returned to normal, and IIMo became 0.06 second.

f. Liver disease: Of 20 cases of cirrhosis of the liver or chronic hepatitis, IIMo duration was 0.05-0.09 second in 11 cases, and 0.10-0.14 second in 9 cases (Fig. 10). Thus, an obvious prolongation is observed in about half of the cases studied. Of the latter 9 cases, the 4 cases which showed a IIMo of 0.10 second had the second heart sound appearing 0.04-0.08 second before the end of the T. It is understood that in these cases a prolongation of isometric relaxation is due to early develop-

ment of the closing of the semilunar valves rather than to a delay in the opening of the mitral valve in regard to the end of the T. The other 5 cases showed a IIMo of 0.11-0.14 second and revealed mostly a delayed opening of the mitral valve.

g. Cases with marked Q-T prolongation: It is interesting to note what changes in mechanical movements are found in cases which show a marked prolongation in an electrical phenomenon. Fig. 11 shows an example of the final stage of angina necroticans in which Q-T covers 0.81 second. The low-frequency Doppler signal which denotes the movements of the heart wall in contraction begins 0.07 second after the beginning of the QRS, and ends 0.34 second after the beginning of the QRS (Fig. 11, *top*). Even that in relaxation ends nearly at the peak of the T. Thus it is suggested that in such cases there would be some parts of the myocardium in which repolarization is locally delayed because of marked myocardial damages. Hence, even when relaxation is almost finished in the greater part of the myocardium, a large abnormal T persists because of such localized delayed repolarization.

The afore-mentioned case, as shown in Fig. 11, *bottom*, reveals an extremely earlier development of the opening of the mitral valve than the end of the T.

In cases such as those of hypopotassemia in which the U wave appears superposed on the end of the T the opening of the mitral valve, as well as the second heart sound, appears earlier.

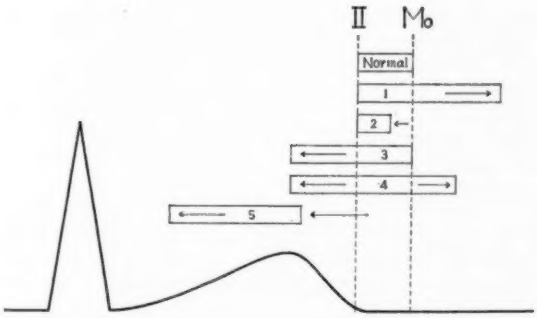

Fig. *12*. Modes of time relationship between opening of the mitral valve, second heart sound, and the end of T. *1*, A delayed opening of the mitral valve. *2*, An early development of the opening of the mitral valve. *3*, An early development of the second heart sound. *4*, Coexistence of *1* and *3*. *5*, Marked Hegglin syndrome.

The correlationship in terms of time between the opening of the mitral valve, closing of the semilunar valves, and electrical events seems to be very much complicated. It is detailed as follows (Fig. 12): (1) delay in the opening of the mitral valve as found in coronary sclerosis, hypertensive heart, etc.; (2) early development of the opening of the mitral valve as found in mitral stenosis and congestive heart failure; (3) early development of the closing of the semilunar valves (second heart sound), i.e., Hegglin syndrome[30]; (4) early development of the second heart sound, and delayed opening of the mitral valve; (5) severe cases of Hegglin syndrome which show a markedly early development of the opening of the mitral valve.

Table IV. *Relationship between ECG and duration of isometric relaxation in cases of mitral stenosis or mitral stenosis and regurgitation* (*number of cases*)

		IIMo (*Second*)						
		0.02	*0.03*	*0.04*	*0.05*	*0.06*	*0.07*	*0.08*
MS	Cases with abnormal ECG	3	9	4	1	5	0	0
(29 cases)	Cases with normal ECG	0	0	3	2	2	0	0
MSI	Cases with abnormal ECG	2	2	1	2	2	0	0
(18 cases)	Cases with normal ECG	2	0	2	0	3	1	1

MS: Mitral stenosis. MSI: Mitral stenosis and regurgitation.

Table V. Time of valvular movements in cases of RBBB and cases of LBBB

	RBBB		LBBB	
	Number of cases	Average (range: in seconds)	Number of cases	Average (range: in seconds)
QMc	15	0.058 (0.04–0.09)	5	0.086 (0.07–0.11)
QTc	9	0.083 (0.07–0.10)	5	0.062 (0.05–0.08)
QAo	14	0.122 (0.10–0.14)	5	0.174 (0.16–0.20)
QPo	11	0.160 (0.14–0.17)	4	0.135 (0.12–0.16)
McAo	14	0.066 (0.04–0.09)	5	0.090 (0.05–0.12)
TcPo	5	0.082 (0.07–0.09)	4	0.070 (0.06–0.10)
IIaMo	15	0.113 (0.06–0.13)	3	0.137 (0.13–0.14)
IIpTo	4	0.103 (0.08–0.12)	4	0.115 (0.10–0.13)

It is understood that the conversion phase from ventricular contraction to relaxation is to be discussed in reference to: (1) its beginning, i.e., the time of development of the second heart sound, and (2) the duration of isometric relaxation.

Suggested in regard to the determination of the length of isometric relaxation are the conditions of the myocardium itself, such as are anticipated to be present in cases of myocardial changes, and passive conditions, such as an increased atrioventricular-pressure difference which is considered in cases of mitral stenosis. It is assumed that the above-mentioned conditions may act simultaneously to determine the duration of isometric relaxation.

h. The time of valvular movements in bundle branch block: The time of movements of each valve was detected in several cases of bundle branch block by the ultrasonic Doppler method. The result is shown in Table V.

Summary

1. The ultrasonic Doppler method has been used to obtain information on the movements of the heart.

2. The time of development of valvular movements is determined; a wide range of variation under various conditions is shown.

3. In cases of coronary sclerosis, hypertension, etc., the opening of the mitral valve is delayed, revealing a prolonged duration of isometric relaxation. The abnormalities develop prior to myocardial change in the ECG.

4. In cases of mitral stenosis the closing of the mitral valve is delayed and the opening is quickened, showing the shortening of isometric relaxation.

5. In cases of mitral valvular disease with auricular fibrillation the shorter the preceding R-R, the more delayed is the closing of the mitral valve.

6. Prolonged isometric relaxation develops even in cases of nephritis, hypothyroidism, liver disease, etc.

7. The time relationship between the opening of the mitral valve, the closing of the semilunar valves, and the end of the T wave is referable to the following modes: (a) a delayed opening of the mitral valve; (b) early development of the opening of the mitral valve; (c) early development of the closing of the semilunar valves (Hegglin syndrome); (d) coexistence of (a) and (c); (e) early development of the opening of the mitral valve subsequent to early development of the closing of the semilunar valves in cases of marked Hegglin syndrome.

REFERENCES*

1. Wild, J. J., and Reid, J. M.: Ultrasonic ranging speeds. Cancer diagnosis, Electronics **28:** No. 3, 174, 1955.
2. Wild, J. J., and Reid, J. M.: The effects of biological tissues on 15 Mc pulsed ultrasound, J. Acoust. Soc. Am. **25:**270, 1953.
3. Ludwig, G. D., and Struthers, F. W.: Detecting gallstones with ultrasonic echoes, Electronics **23:** No. 2, 172, 1950.
4. Kikuchi, Y., Uchida, K., Tanaka, R., and Wagai, T.: Early cancer diagnosis through ultrasonics, J. Acoust. Soc. Am. **29:**824, 1957.
5. Tanaka, R., Wagai, T., Kikuchi, Y., and Uchida, K.: Choonpa ni Yoru Zugai-nai-shikkan no

*Translation of the Japanese titles is tentatively being done by the present authors.

Kenshutsu ni tsuite: I (On detecting intracranial diseases with ultrasonics: I), J. Jap. Surg. Soc. **54**:242, 1952.

6. Fukuda, T., Tanaka, R., and Wagai, T.: Choonpa no Shindan e no Oyo (Ultrasonics applied in clinical diagnosis), J. Jap. Acoust. Soc. **13**:37, 1957.
7. Yamakawa, K.: Fukkokyo ni Yoru Fukkonai-zoki-satsuei no Kenkyu (A study on photographing intra-abdominal organs with laparoscope), Lecture at the 44th Annual Meeting of the Gastroent. Soc. Jap. **13**:37, 1957.
8. Keidel, W. D.: Über eine neue Methode zur Registrierung der Volumveränderungen des Herzens am Menschen, Ztschr. Kreislaufforsch. **39**:257, 1950.
9. Edler, I., and Hertz, C. H.: The use of ultrasonic reflectoscope for the continuous recording of the movement of heart walls, Kungl. Fysiografiska Sällskapets I Lund Förhandlingar. **24**: Nr. 5, 1, 1954.
10. Edler, I., and Gustafson, A.: Ultrasonic cardiogram in mitral stenosis, Acta med. scandinav. **159**:85, 1957.
11. Hertz, C. H., and Edler, I.: Die Registrierung von Herzwandbewegungen mit Hilfe des Ultraschallimpulsverfahren, Acustica **6**:1, 1956.
12. Wild, J. J., Crawford, H. D., and Reid, J. M.: Visualization of the excised human heart by means of reflected ultrasound or echography, Am. Heart J. **54**:903, 1957.
13. Biquard, P.: Les ultrasons, Paris, 1948, Presses Universitaires de France.
14. Hueter, T. F., and Bolt, R. H.: Sonics, New York, 1955, John Wiley & Sons, Inc.
15. Satomura, S.: Ultrasonic Doppler method for the inspection of cardiac functions, J. Acoust. Soc. Am. **29**:1181, 1957.
16. Satomura, S.: Choonpa Doppler-ho ni Yoru Shinzo-kino-kensa no Kenkyu: I. Genri; II. Sochi (A study on examining the heart with ultrasonics: I. Principle; II. Instrument), Jap. Circul. J. **20**:227, 1956.
17. Yoshida, T., Mori, M., Nimura, Y., Okimura, M., Hikita, G., Nakanishi, K., and Satomura, S.: Choonpa Doppler-ho ni Yoru Shinzokino-kensa no Kenkyu: III. Doppler-ho no Shurui; IV. Rinsho-teki-oyo (A study on examining the heart with ultrasonics: III. Kinds of Doppler beats; IV. Clinical application), Jap. Circul. J. **20**:228, 1956.
18. Yoshida, T., Mori, M., Nimura, Y., Takagishi, S., and Nakanishi, K.: Shinzo ni Okeru Choonpa-shindan-ho no Oyo (Ultrasonics clinically applied in examining the heart), Sogorinsho **8**:591, 1959.
19. Takagishi, S.: Valvular movements in the cardiac cycle defined by the ultrasonic Doppler method, Med. J. Osaka Univ. (Japanese edition) **11**:5317, 1959.
20. Yoshida, T., Mori, M., Nimura, Y., Takagishi, S., and Nakanishi, K.: Choonpa ni Yoru Shin-kino-kaiseki to Shin-on (An analysis of cardiac function with ultrasonics in reference to heart sound), Nippon-rinsho **17**:143, 1959.
21. Hikita, G., Nakanishi, K., Okimura, M., Takagishi, S., Nimura, Y., Mori, M., Yoshida, T., Yoshioka, M., Matsubara, S., and Satomura, S: Choonpa Doppler-ho ni Yoru Shinzo-kinokensa no Kenkyu: V. Ben no Doppler-on ni Tsuite (A study on examining the heart with ultrasonics: V. Doppler beats due to valves), Jap. Circul. J. **20**:625, 1956.
22. Nimura, Y.: A vectorcardiographic analysis of left ventricular strain pattern comparatively studied with ST-T change of left bundle branch block and ventricular premature beat of right ventricular origin, Am. Heart J. **57**:552, 1959.
23. Yoshida, T., Nimura, Y., Mori, M., Nakamura, K., Okimura, M., and Shirai, J.: On vectorcardiogram: VII. Clinical study on types of ST-T change, Jap. Circul. J. **19**:198, 1955.
24. Nakanishi, K.: Study on the valvular movement in mitral valvular disease by the ultrasonic Doppler method, Med. J. Osaka Univ. (Japanese edition) **11**:4549, 1959.
25. Wells, B.: The assessment of mitral stenosis by phonocardiography, Brit. Heart J. **16**:261, 1954.
26. Kelley, J. J.: Diagnostic value of phonocardiography in mitral stenosis. Mode of production of first heart sound, Am. J. Med. **19**:862, 1955.
27. Yamakawa, K., Yamamoto, T., Ohta, S., and Kitamura, K.: Problem of delayed start of the first sound in mitral stenosis, Jap. Circul. J. **18**:127, 1954.
28. Ueda, H., Yoshimura, S., Kaito, G., Sugai, J., Yamadera, T., Hara, Y., Hashimoto, H., Sato, Y., and Sato, F.: Genesis of the first heart sound. Viewed from hemodynamics and its clinical significance, Jap. Circul. J. **21**:170, 1957.
29. Rosenberg, S. Z., Eliakim, M., and Braun, K.: Relationships between electrical and mechanical events in atrial fibrillation. A study of direct atrial pressure tracings, Am. Heart J. **53**:18, 1957.
30. Hegglin, R.: Die Energetisch-dynamische Herzinsuffizienz. Eine besondere Form der Myokardschwäche, Schweiz. med. Wchnschr. **74**: 1104, 1944.

The experimental induction of myocardial infarction

A. L. Myasnikov, Ph.D.
N. N. Kipschidze, M.D.
E. I. Tchazov, M.D.
Moscow, U.S.S.R.

Myocardial infarction may be induced experimentally by ligating one of the coronary arteries, or by embolization of a coronary artery with a foreign material, such as liquapodium or glass beads. It is evident, however, that these methods do not correspond to the actual conditions under which myocardial infarction occurs in man. In man, myocardial infarction generally develops as a result of arteriosclerotic changes in the wall of the coronary arteries. In addition, functional factors, such as myocardial stress, spasm of the coronary arteries, and biochemical changes, play a role in the pathogenesis of myocardial infarction.

We have undertaken to produce experimental myocardial infarction in rabbits without resorting to the mechanical methods generally utilized to obstruct the supply of blood to cardiac muscle. Instead, those factors were utilized which are generally considered to contribute to the development of myocardial infarction in man.

Experimental method

Coronary atherosclerosis was induced in rabbits by the administration of cholesterol in the diet for 6 months according to the method of Anichkov. These cholesterol-fed animals were subjected to additional factors which, from the clinical point of view, were considered to contribute to the development of myocardial infarction. These additional factors included myocardial stress, altered blood coagulability, and coronary arterial spasm.

1. Twenty-two animals were made arteriosclerotic by feeding them cholesterol but were not subjected to any other influences considered to produce myocardial infarction.

2. Twenty-five cholesterol-fed animals were subjected to strenuous physical exertion so as to produce myocardial stress. Eight animals were subjected to the same physical stress but were not fed cholesterol.

3. Fifteen animals which had been fed cholesterol for 120 days were given single small doses of thrombin intravenously. Each of 8 animals which had not been fed cholesterol received a single small dose of thrombin intravenously.

4. To each of 10 healthy animals a single intravenous dose of Pituitrin alone was given, whereas an additional 21 healthy animals were given single doses of intravenous Pituitrin and thrombin in combination.

5. Animals which had been fed cholesterol for 2 months were given single doses of Pituitrin and thrombin separately and in combination.

Results

Cholesterol feeding alone. None of the animals which were fed diets high in cholesterol, but which were not subjected to additional influences, developed acute myocardial infarction (Table I). These animals developed marked atherosclerosis of the

Received for publication May 16, 1960.

aorta and coronary vessels, but in spite of narrowing of the lumens of the coronary arteries, myocardial infarction did not occur. Only small areas of fibrosis were found in the myocardia, especially in the intramural branch of the left coronary artery (Figs. 1 and 2).

Cholesterol feeding plus physical stress. Twenty-five cholesterol-fed animals were subjected to intensive physical exercise in order to impose a stress on the myocardium. The animals were made to run on a treadmill for 1 hour daily during the entire period of cholesterol feeding. Serial electrocardiograms showed progressive signs of coronary failure. In most of the animals, episodes of cardiac asthma developed periodically and persisted to the end of the experiment. Some of the animals died in the fourth and fifth months, i.e., they did not survive the 6-month experimental period. At necropsy, large areas of myocardial necrosis (Fig. 3) and scarring (Fig. 4) secondary to arteriosclerotic changes were found in all of the animals. Inflammatory reaction in the perinecrotic areas, a characteristic of myocardial in-

Table I

Experimental conditions	*Number of animals*	*Number of animals with myocardial infarction (necrobiosis of heart muscle)*
1. Cholesterol feeding alone	22	0
2. Cholesterol feeding plus physical stress	25	25
Physical stress alone	8	0
3. Cholesterol feeding (120 days) and administration of thrombin	15	10
Administration of thrombin to healthy animals	8	0
4. Administration of Pituitrin to healthy animals	10	0
Combined administration of Pituitrin and thrombin to healthy animals	21	17
5. Short-term cholesterol feeding (70 days) and combined administration of Pituitrin and thrombin	16	14

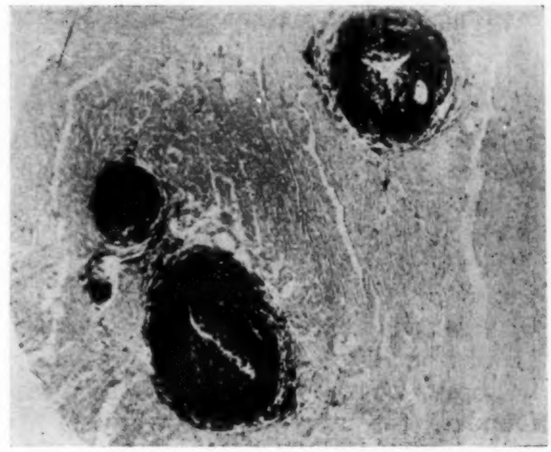

Fig. *1.* Cholesterol feeding only. Note that arteriosclerotic plaques almost completely obliterate the lumens of the intramuscular branches of the left coronary artery (Sudan III).

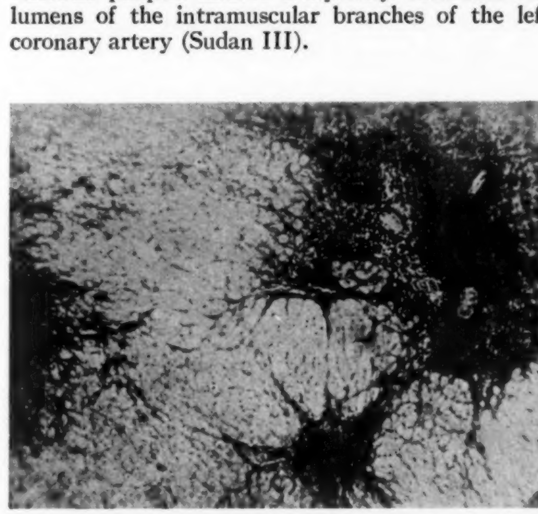

Fig. *2.* Cholesterol feeding only. Note the connective tissue scars (myocardial fibrosis) in the anterior wall of the left ventricle (Mallory's method).

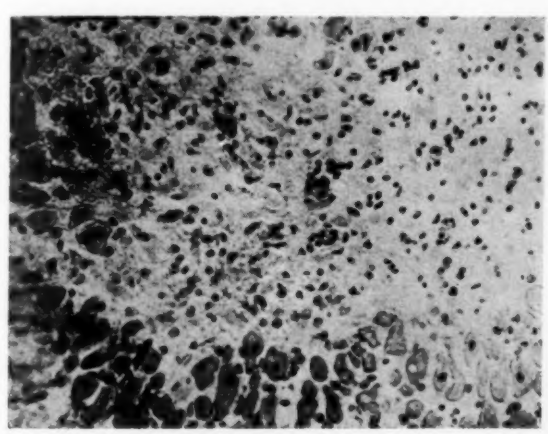

Fig. *3.* Cholesterol feeding plus physical stress. Note the large focus of myocardial necrosis and the round cell infiltration in the perinecrotic area (hematoxylin-eosin).

farction, was noted (Fig. 3). In several rabbits, aneurysm of the left ventricle had developed (Fig. 5). Thrombosis was not found in any animal. The areas of necrosis were distributed throughout the anterior, lateral, posterior, and septal walls of the left ventricle and in the papillary muscles. (See Fig. 6.)

In the control group of 8 animals subjected to the same physical stress, but without cholesterol feeding, moderate left ventricular hypertrophy was noticed at necropsy, but no areas of necrosis were found in the myocardium in any of the animals (Table I).

COMMENT. According to this data, physical stress in the presence of coronary atherosclerosis is important in the pathogenesis of myocardial infarction.

Fig. *4*. Cholesterol feeding plus physical stress. Note the dense scar found in tissue removed from the posterior wall of the left ventricle (pycrofuchsin).

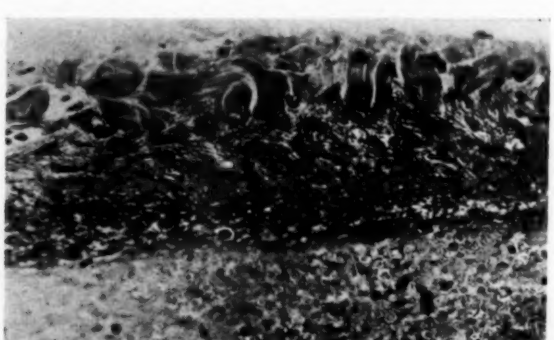

Fig. *5*. Cholesterol feeding plus physical stress. The section was taken from the wall of an aneurysm of the left ventricle (pycrofuchsin).

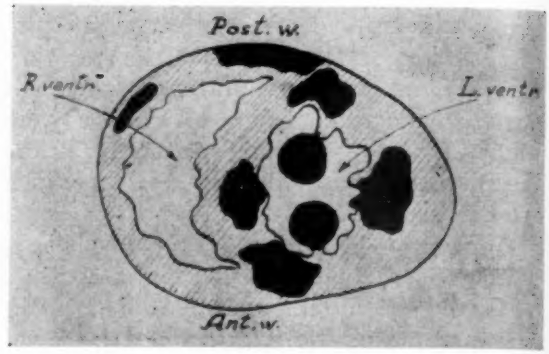

Fig. *6*. Cholesterol feeding plus physical stress. Coronal section of the entire heart of an animal with multiple myocardial infarcts. The black areas represent the sites of myocardial infarction.

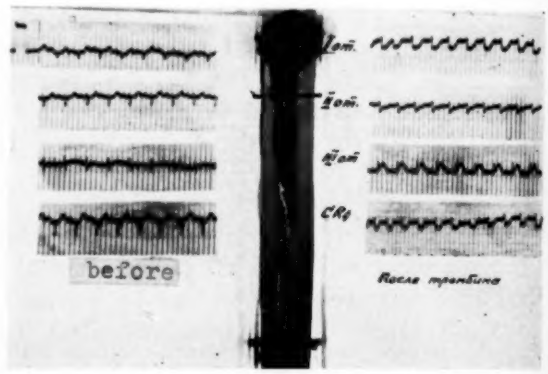

Fig. *7*. Cholesterol feeding plus administration of thrombin. Electrocardiographic changes before and after the administration of a single dose of thrombin. Note the depression of the S-T segment in Leads I, II, and CR_4, and the elevation of the S-T segment in Lead III after thrombin was given.

Cholesterol feeding plus administration of thrombin. Cholesterol-fed animals were administered a single small dose of thrombin intravenously. The animals were given 3-4 c.c. of thrombin (activity, 12 seconds*), a dose which in 8 healthy animals did not produce coronary thrombosis (Fig. 10, Table I). In the rabbits made arteriosclerotic by cholesterol feeding, such small doses of thrombin led to formation of thrombosis and myocardial infarction in 10 of 15 animals (Figs. 7, 8, and 9).

COMMENT. These experiments indicate that changes in the coagulability of blood play a definite role in the pathogenesis of myocardial infarction.

*The activity of thrombin solution was determined according to the time which was necessary for clotting: 0.1 ml. oxalated blood by 0.1 ml. thrombin solution at 32° was clotted in 1 second.

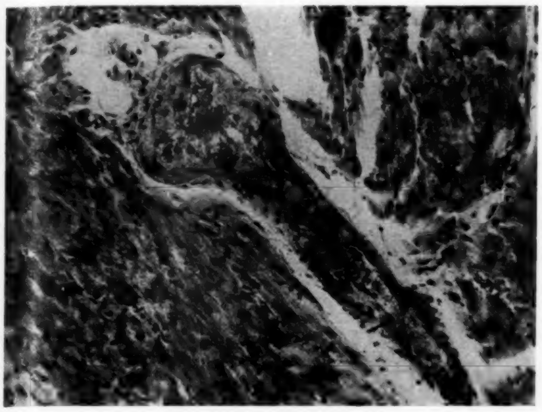

Fig. 8. Cholesterol feeding plus thrombin. Note the thrombus obliterating one of the branches of the left descending coronary artery in the same animal whose electrocardiogram is shown in Fig. 7. (Objective 20X, ocular 7X.)

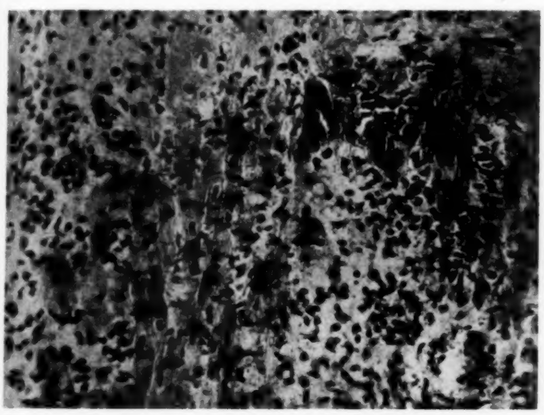

Fig. 9. Cholesterol feeding plus thrombin. The myocardial necrosis and lipoidosis of the blood vessels occurred after the administration of 3.0 c.c. of thrombin intravenously. (Objective 20X, ocular 7X.)

Combined administration of Pituitrin and thrombin to healthy animals. In another group of animals the role of coronary spasm in the pathogenesis of myocardial infarction was studied. Pituitrin (and in 8 experiments, barium chloride) was used to produce coronary arterial spasm. The intravenous administration of 0.3 to 0.5 c.c. of Pituitrin did not produce any significant changes in the electrocardiograms of 10 healthy animals, and at necropsy no areas of necrosis were found in these animals. Additional experiments were carried out in which Pituitrin and thrombin were administered together to healthy animals. This was done in order to investigate the possibility of producing acute coronary failure in the absence of coronary atherosclerosis under the influence of two factors, namely, spasm and altered coagulability of the blood. The combined administration of Pituitrin and thrombin did result in electrocardiographic changes typical of an acute disturbance of the coronary circulation in 17 of 21 animals (Fig. 10, Table I). At necropsy there were thrombi in the coronary vessels (Fig. 11), myocardial ischemia, and, in animals which lived long enough (3 to 5 days), histologic changes such as are seen in myocardial infarction (Fig. 12).

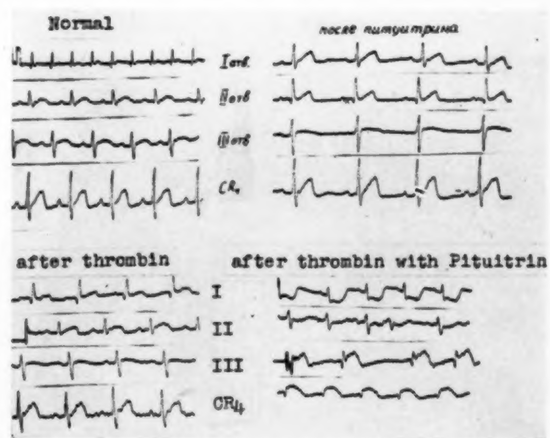

Fig. 10. Combined administration of Pituitrin and thrombin to a healthy animal. Note that the administration of thrombin alone resulted in essentially no changes in the electrocardiogram, whereas the administration of Pituitrin and thrombin in combination resulted in electrocardiographic changes consistent with acute posterior myocardial infarction.

Fig. 11. Combined administration of Pituitrin and thrombin to a healthy animal. Note the thrombus obliterating one of the branches of the left descending coronary artery. The animal was given 4.0 c.c. of thrombin and 0.5 c.c. of Pituitrin intravenously. (Objective 20X, ocular 7.5X.)

COMMENT. These results indicate that coronary arterial spasm in association with altered coagulability of the blood can lead to the formation of thrombus and myocardial infarction without organic involvement of the arterial wall by arteriosclerosis.

Administration of thrombin and/or Pituitrin to slightly arteriosclerotic animals. The administration of thrombin or Pituitrin alone to animals made slightly arteriosclerotic by short-term cholesterol feeding (2 months) did not result in myocardial infarction. However, the combined administration of thrombin and Pituitrin produced electrocardiographic and morphologic evidence of myocardial infarction (Fig. 13) and aneurysmal formation (Fig. 14, Table I).

Fig. *12.* Combined administration of Pituitrin and thrombin to a healthy animal. Myocardial necrosis found at necropsy in an animal to whom 4.0 c.c. of thrombin and 0.5 c.c. of Pituitrin had been administered intravenously.

Fig. *13.* Combined administration of Pituitrin and thrombin to a slightly arteriosclerotic animal. Longitudinal section of coronary blood vessels. The lumen of the vessel on the right is obliterated by a thrombus. The vessel on the left is patent. The animal was fed cholesterol for 35 days and received 3.0 c.c. of thrombin and 0.3 c.c. of Pituitrin intravenously.

Fig. *14.* Combined administration of Pituitrin and thrombin to a slightly arteriosclerotic animal. Fresh specimen of the heart, showing a ventricular aneurysm.

Conclusions

1. A method for inducing myocardial infarction which more closely approximates the clinical conditions under which myocardial infarction develops in man has been described.

2. It has been shown that atherosclerosis of the coronary arteries is the most significant but not the sole factor in the pathogenesis of myocardial infarction.

3. The important role played by three additional factors in the development of myocardial infarction has been confirmed experimentally. These factors are: (a) myocardial stress, (b) altered coagulability of blood, and (c) spasm of the coronary arteries.

Practical limitations of the Kety method for determining coronary blood flow by infrared analysis of blood nitrous oxide

Ivan E. Forte, M.S.
Louis Potgieter, Ch.B.
*Jerry E. Schmitthenner, M.D.**
Hunter Neal, M.D.
J. H. Hafkenschiel, M.D.
Philadelphia, Pa.

Fifteen years of experience on the part of one of us (J.H.H.) with the nitrous oxide method, using both manometric and infrared analyses of blood gas, has led us to the viewpoint expressed by Lord in an editorial earlier this year. This stressed the fact that the greatest need in the area of diagnostic studies in patients with coronary artery disease "is the development of a precise test to measure coronary arterial blood flow in the human."[1] The lack of such a precise test seems to be an important limiting factor in the selection of patients for, and, hence, the survival rate of those undergoing, endarterectomy. Preliminary reports suggest that endarterectomy is one of the most promising surgical procedures for the alleviation of the disability of angina pectoris by increasing the flow of blood through the myocardium.[2]

The complexity of the Kety–Van Slyke manometric method of analysis of nitrous oxide in the blood may have impeded its widespread utilization for determination of regional flows.[3] In particular, the approximate 5 per cent error in analysis as described by Gregg[4] has raised the question whether this indirect method of nitrous oxide analysis for coronary blood flow measurements is now the best approach. In 1953, Lawther and Bates[5] proposed a direct method of measuring nitrous oxide in blood, using infrared absorption. A recent summary of applications of the nitrous oxide method for determining coronary blood flow in man was presented by Rowe,[6] but no mention was made of the direct method of measuring nitrous oxide in blood by infrared analysis in this review. Bing[7] did not discuss the accuracy to be expected with the manometric nitrous oxide blood gas analytical procedure in his "Determination of Coronary Blood Flow," and did not refer to the direct method of measuring nitrous oxide in blood by infrared absorption.

Preliminary to attempting development of a simpler method of measuring coronary

With the assistance of A. Jane Williams, A.B., Toussef Shakashir, M.D., Robert Richards, M.D., and Cecilia Riegel, Ph.D.
From the Division of Research, Lankenau Hospital, Philadelphia, Pa.
This investigation was supported in part by a research grant (H1817) from the National Heart Institute, Public Health Service, and in part by grants from the Tobacco Industry Research Committee (QH17), and the Committee on Problems of Alcohol of the National Academy of Sciences—National Research Council (UV25), Ciba Pharmaceutical Products, Inc., and the Heart Association of Southeastern Pennsylvania.
Received for publication May 16, 1960.
*Postdoctoral Research Fellow of the National Heart Institute (HF6498) at Lankenau Hospital, 1956-1958.

blood flow applicable to both intact animals and man, it was first necessary to have our team at Lankenau Hospital familiar with the limitations of the nitrous oxide manometric as well as the direct infrared analysis techniques. It was expected that the new method, using the radioactive isotope-dilution principle, could be quantitated by comparison with nitrous oxide measurements of coronary blood flow made simultaneously.[8] This had been done when the indirect nitrous oxide method was calibrated against simultaneous direct measurement of coronary blood flow by means of a bubble flow meter.[9]

The present progress report details the experience of the Lankenau group with the infrared absorption technique from 1953 through 1959, in making paired observations of coronary blood flow on anesthetized but otherwise intact dogs, using the techniques of Eckenhoff and co-workers.[9-13] Particular attention is given to: (1) a comparison of the precision of our measurement of the blood nitrous oxide concentration by means of the infrared absorption spectra of nitrous oxide with the precision acquired by analysts using the Van Slyke manometric technique, and (2) a comparison of our experience with the results reported by Foltz,[10] using successive measurements of coronary blood flow in dogs under combination anesthesia.

Methods

Our objective at Lankenau Hospital was to establish the reproducibility of an experimental design in which the same animals were tested repeatedly, using the combined anesthesia, morphine Dial-urethane pentobarbital (MDUP). Since our preliminary report[14] in 1955, only minor changes have been made in the technique for measuring by infrared analysis blood nitrous oxide.*

Results

1. Measurement of nitrous oxide gas by infrared absorption. The technique was reported by Lawther and Bates.[5] Before their paper was published, arrangements were made with an American firm* to make available a unit which has been in more or less continuous use in our laboratory. Lawther and Bates had used an instrument manufactured in England.

Our instrument has required some maintenance and tuning. The constancy of the instrument was tested with calibrating mixtures. Of interest in relation to the reproducibility of the physical instrument is our observation that an unknown gas containing approximately 740 parts per million (p.p.m.) of nitrous oxide, measured on eleven different days between April, 1955, and July, 1957, yielded readings varying between 723 and 756 p.p.m. when compared with a standard gas containing 670 p.p.m. of nitrous oxide.

2. Measurement of nitrous oxide in blood. The method used is essentially the same as that of Lawther and Bates.[5] However, a dual extraction apparatus has been devised in order to save time in analyzing the pairs of arterial and coronary venous samples. The procedure used to get the nitrous oxide out of the blood and to pass as a gas through the infrared analyzer follows the steps described by Lawther and Bates.

The results with this method, using human blood in which two different concentrations of nitrous oxide have been dissolved, are shown in Table I. Two concentrations were decided upon: 2.36 ml. per 100 ml. of blood, which would be a small amount for either a human cerebral or coronary blood flow; and 7.65 ml., which would be a large amount. When our results are compared with those of Lawther and Bates (Table I), their analytical precision is not confirmed. The two co-workers in our laboratory have essentially the same degree of precision.

3. Results of duplicate determinations of blood nitrous oxide gas when the nitrous oxide concentration is varied. Since there are slight differences between human and dog blood, we compared the per cent error of the analysts using the infrared technique *in dog blood only* with the results of the most experienced Van Slyke manometric analyst in our laboratory. These observations are

*Details of the method have been mimeographed and are available by writing to the senior author. This summary includes the steps involved in performing the animal studies from anesthesia to long-term care by our veterinarian.

*The instrument used is the Model 15 Nitrous Oxide Analyzer made by the Liston Becker Division of Beckman Instruments, Inc.

Table I. Infrared blood gas analyzer. Reproducibility of method of measuring nitrous oxide content of blood

	Observers				
	Lawther and Bates, 1953	Lankenau #1, 1960		Lankenau #2, 1960	
		A	B	A	B
Mean of 20 determinations (ml. N_2O per 100 ml. blood)	4.36 ml./100 ml.	2.36	7.65	2.38	7.55
Range	4.34-4.38	2.20-2.49	7.31-7.82	2.18-2.44	7.32-7.70
Standard deviation of individual differences	0.012	±0.07	±0.11	±0.07	±0.08
Coefficient of variation	±0.274%	3.0%	1.4%	2.9%	1.1%

recorded in Table II, with the manometric analyses shown under *Observer #4*.

This observer had "errors" which ranged from 18 to 2 per cent; "error" was defined as the standard deviation in volume per cent divided by the average range in volume per cent, the smallest standard deviation being ±0.09 volume per cent. Kennedy,[15] using human blood, reports a standard deviation of ±0.009 volume per cent with the Kety modification and standard deviation of ±0.025 volume per cent with his micromethod.

Three different observers used the infrared analysis method, and all three had the same standard deviation (i.e., ±0.20 to 0.25 volume per cent) over the range tested. This standard deviation compared favorably with the manometric technique in our laboratory, the over-all per cent error being 4-5 per cent for both methods. The time saved through the use of the infrared method has been approximately 25 to 33 per cent.

4. Errors involved in determining the arteriovenous differences of blood nitrous oxide concentrations in applying the desaturation method of measuring coronary blood flow. The purpose of this analysis was to compare our data with those reported by Gregg[4]: "In the nitrous oxide procedure, the technical error in determining the nitrous oxide arteriovenous difference can be judged from the fact that the average difference of duplicate nitrous oxide analyses for the 120 pairs was 0.030 volumes per cent, the maximum difference being 0.065 volumes per cent. Such differences can possibly introduce an error approximating 5 per cent, since the mean nitrous oxide arteriovenous difference during a test run varied in different experiments from 0.55 to 1.5 volumes per cent, with an average difference of 0.8 volumes per cent."

In order to analyze our data for comparison in the same flow range as Gregg, i.e., 40 to 150 c.c., we graphed the twenty-one coronary blood flow curves determined by infrared arteriovenous nitrous oxide differences within the range of 40 to 150 c.c./100 Gm./minute, and twelve resulting from a Van Slyke manometric analysis of blood gas. All data were derived from observations of coronary blood flow made in the dogs under morphine Dial-urethane pentobarbital anesthesia (MDUP) in control studies.

The average arterial nitrous oxide (N_2O) concentrations for 1, 2, 4, 6, 8, and 10 minutes of the desaturation curves were plotted along with the same points on the coronary venous curves giving average arteriovenous values. These values are shown in Table III.

The standard deviation given is that of the infrared analysis or manometric technique in the various ranges of blood N_2O in cubic centimeters per 100 c.c. blood. The per cent error is the standard deviation divided by the average arteriovenous value.[16] This table shows that the percentage error tends to increase, reaching the greatest level at the tenth minute. Since the coronary blood flow value is heavily weighted by the denominator, which is the integrated arteriovenous difference, the precision of the analytical method is of practical importance.

Table II. *Results of duplicate determinations of dog blood with varying concentrations of nitrous oxide*

	Observer #1			*Observer #2*			*Observer #3*			*Observer #4*†		
Range (ml./100 ml. blood)	*Number of duplicate observations*	*S.D.*	*Per cent error**	*Number of duplicate observations*	*S.D.*	*Per cent error*	*Number of duplicate observations*	*S.D.*	*Per cent error*	*Number of duplicate observations*	*S.D.*	*Per cent error*
0–1	3	0.12	24	4	0.06	12	2	—	—	7	0.09	18
1–2	27	0.20	13	15	0.25	17	10	0.05	3	26	0.23	15
2–3	28	0.22	9	11	0.23	9	12	0.10	4	17	0.38	15
3–4	7	0.31	9	5	0.28	8	5	0.12	3	12	0.22	6
4–5	12	0.09	2	7	0.15	3	3	0.30	6	33	0.14	3
5–6	13	0.37	7	37	0.31	6	1	—	—	45	0.13	2
6–7	53	0.27	4	52	0.23	4	16	0.27	4	6	0.20	3
7–8	59	0.25	3	15	0.19	3	57	0.17	2	1	—	—
8–9	1	—	—	—	—	—	1	—	—	—	—	—
9–10	—	—	—	—	—	—	1	—	—	—	—	—
Total range 0–10	203	0.25	5	146	0.25	5	108	0.20	4	147	0.20	4

*Per cent error: $\frac{\text{Standard deviation in volume per cent}}{\text{Average range in volume per cent}}$

†These determinations were made using Kety's modification of the Orcutt-Waters method using the Van Slyke manometric apparatus.

5. *Measurements of coronary blood flow in anesthetized dogs.*

A. FIRST STUDIES COMPLETED IN 53 DIFFERENT EXPERIMENTS ON 14 DOGS. Foltz and co-workers,[10] in 1950, had reported that, depending upon the anesthesia used (pentobarbital or MDUP), quite different levels of cardiac activity were obtained: "Both anesthetic agents show rather wide standard deviations for the population, which we have interpreted as indicative of rather wide biological variation between animals, but which also represent undoubtedly a considerable variation in response to anesthesia."

Because repeat measurements of coronary blood flow in human beings at later times are unlikely, and because our application of the method permitted recovery of an animal after the study, we decided to extend the Foltz investigation by making successive observations on a lesser number of dogs. The purpose was to determine how reproducible our measurements of the levels of coronary flow might be, using infrared analysis of blood nitrous oxide, with simultaneous measurements of cardiac oxygen metabolism, cardiac rate and work.

The results are summarized in Table IV. Under the combination anesthesia (MDUP)* the mean flow values were 91 c.c., standard deviation ±33, and coefficient of variation ±36 per cent. The flow values measured under the combination anesthesia are essentially the same as reported by Foltz and associates[10] (Table III). We observed slightly higher levels of coronary flow, cardiac arteriovenous oxygen extraction, and cardiac work. When MDUP anesthesia was used, the mean cardiac rate was 74, with a standard deviation of ±25, and when pentobarbital was used, it was 162, with a standard deviation

*The technique is as follows: The total dose of morphine is 3.0 mg. per kilogram. Two thirds of the initial dose is given subcutaneously 45 minutes before the intravenous injection. This consists of equal parts by volume of pentobarbital (65 mg./c.c.) and the Dial-urethane mixture, the total being 0.30 c.c. per kilogram, i.e., 0.15 c.c. of pentobarbital and 0.15 c.c. of Dial-urethane. This is supplied by Ciba Pharmaceutical Products, Inc. About 1 to 1½ hours after the intravenous dose, the animal having been operated upon and the catheters placed properly, 1/6 of the total dose is given intramuscularly 30 minutes before the infusion of saline for the first measurement of coronary blood flow and cardiac output. Just after this study is completed, and approximately 30 minutes before observation #2, a comparable dose of morphine is given again intramuscularly. This is usually 20 minutes before any drug stimulus is introduced.

of ±19. The most striking difference was a standard deviation in coronary flow values three times that reported by Foltz in his pentobarbital series. This shows that in a group of 6 dogs with 28 different observations, as compared to Foltz' observations (19) in 19 dogs, we have observed similarly "rather wide biological variation." Thus, we have confirmed Foltz' observations, by means of another method of quantitating the nitrous oxide in blood, that coronary blood flow and cardiac oxygen uptake are greater under pentobarbital anesthesia, the heart rate being more than twice as rapid.

B. COMPARISON OF MEAN VALUES FOR 37 CORONARY BLOOD FLOW OBSERVATIONS IN SAME DOGS AFTER SHORT AND LONG INTERVAL. This analysis was made in an attempt to discover whether the variation in coronary blood flow and cardiac oxygen consumption was due to "wide biological variation between animals"[10] or to some factor inherent in the lability of coronary blood flow. These observations were carried out in fewer dogs. All observations made under the same anesthesia, when a drug was not being studied, were compared. The data are presented in Table V and show the mean values of the first run compared with the mean values of the second run in the 8 dogs (37 comparisons) under the combination anesthesia. Under this (MDUP) anesthesia the variation in coronary blood flow at four-week intervals was essentially the same as that recorded when the observations were repeated after 30 to 40 minutes.

Discussion

We conclude that in our laboratory the infrared analytical technique is not so precise as that reported by Lawther and Bates, and does not approach the rigorous requirements for manometric analysis set up by Kety[3] and met by Gregg.[4] However, this method does save 25 to 33 per cent of time as compared with the manometric technique, and the "per cent error" is about the same as that of the most experienced Van Slyke analyst in our laboratory. The percentage figure above for reduced analytical time included the time required for another blood gas analysis if a single one of the five paired nitrous oxide blood concentrations did not fall on a smooth curve drawn for the flow, thus requiring a recheck.[3]

The most obvious factor other than biological variation which might be causally related to the large percentage coefficient of variation in coronary blood flow measurements using nitrous oxide is the blood gas analytical method. Our results are interpreted as indicating that the infrared analytical method must be further improved in order to reduce the technical error recorded here in determining the nitrous oxide arteriovenous oxygen difference. It would seem that this is a twofold problem, requiring greater skill on the part

Table III. *Average arteriovenous differences of nitrous oxide during 10-minute period of desaturation*

	Morphine Dial-urethane pentobarbital anesthesia					
	Van Slyke manometric analysis			*Infrared analysis*		
	12 Coronary flows (40-150 c.c./100 Gm./min.)			*21 Coronary flows (40-150 c.c./100 Gm./min.)*		
	Average A-V	*S.D.*	*Per cent error**	*Average A-V*	*S.D.*	*Per cent error*
First min.	1.70	0.20	11.8	1.76	0.26	14.8
Second min.	1.54	0.24	15.6	1.59	0.23	14.5
Fourth min.	0.80	0.28	35.0	0.90	0.20	22.2
Sixth min.	0.39	0.21	53.9	0.50	0.19	38.0
Eighth min.	0.24	0.21	87.6	0.29	0.17	58.6
Tenth min.	0.14	0.09	64.3	0.11	0.17	155

Average A-V: c.c.N_2O/100 c.c. blood.
Standard deviation is that of the method of analysis in the various ranges of blood N_2O in c.c./100 c.c. blood.
Per cent error: S. D. divided by average A-V.

Table IV. First studies completed in 53 different experiments on 14 dogs weighing from 26 to 48 kilograms

	Coronary blood flow (c.c./100 Gm./min.)		
	Mean	S.D.	Per cent coefficient of variation
Pentobarbital anesthesia*	175	73	42
Morphine Dial-urethane pentobarbital anesthesia†	91	33	36

*28 different experiments on 6 dogs.
†25 different experiments on 8 dogs.
S.D.: Standard deviation of the individual differences from the mean difference.
Per cent coefficient of variation The ratio of the standard deviation of the individual difference to the initial mean value of the parameter.

Table V. Comparison of mean values for 37 coronary blood flow observations in same dogs after short and long interval

	Coronary blood flow (c.c./100 Gm./min.)			
	Observation period		S.D. differences	Per cent coefficient of variation
	1	2		
Morphine Dial-urethane (30-40 min.)	94	90	25	26
Pentobarbital anesthesia (4 weeks)	86	76	27	31

S.D. difference: Standard deviation of the individual differences from the mean difference.
Per cent coefficient of variation: The ratio of the standard deviation of the individual difference to the initial mean value of the parameter.

of the analyst and better instrumentation, so that the results reported by Lawther and Bates (Table I)[5] might be approached in this hemisphere.

Even though analytical precision is improved, spurious and erroneous results may develop when the nitrous oxide method is used for measuring regional blood flow in biological systems, as pointed out by Sapirstein.[17] With infrared analysis, no experiments had to be discarded either because of failure to obtain smooth curves or because the final arteriovenous nitrous oxide difference was greater than 0.3 volume per cent, the level above which most workers agree that discard is indicated. During the period covered in this report, only three flows, involving the manometric technique of nitrous oxide analysis, were discarded.

From this survey of the precision of our analytical methods, and from the negative results obtained from the application of the radioisotope-dilution technique developed in this laboratory,[8] it is evident that there is still need for devising a simpler method of measuring coronary blood flow in animals; and Bing and associates[18] have recently reached the same conclusion with reference to human beings.

Summary

This report provides data bearing on inconstancies and, perhaps, inaccuracies which are present when the nitrous oxide method is applied in the measurement of regional blood flows, such as coronary blood flow.

The manometric technique used for eight years in a study of both cerebral and coronary blood flow was replaced by infrared nitrous oxide blood gas analysis during the past seven years. The limitations of this method are categorized under these headings: (1) measurement of nitrous oxide gas by infrared absorption; (2) measurement of nitrous oxide gas in blood; (3) results of duplicate determinations of blood nitrous oxide gas at a low and a high blood nitrous oxide concentration; (4) errors involved in determining the arteriovenous differences of blood nitrous oxide concentrations; and (5) applications of the Kety nitrous oxide desaturation method to measurements of coronary blood flow in anesthetized intact dogs on successive occasions.

We conclude (1) that the blood analytical technique using the principle of infrared absorption is practical, time saving, and comparable in precision to the manometric method, and (2) that during steady states the Kety nitrous oxide test is quantitative and reproducible, and, at the present time, is the best method of measurement of coronary blood flow in intact animals.

REFERENCES

1. Lord, J. W., Jr.: Surgery for coronary artery disease, Surg. Gynec. & Obst. **110**:746, 1960.
2. Longmire, W. P., Jr., Cannon, J. A., and Kattus, A. A.: The surgical treatment of angina pectoris, A. M. A. Arch. Int. Med. **104**:886, 1959.
3. Kety, S. S.: The quantitative determination of cerebral blood flow in man, Methods in Medical

Research, Vol. 1, Chicago, 1948, Year Book Publishers, Inc., p. 204.

4. Gregg, D. E., Longino, F. H., Green, P. A., and Czerwonka, L. J.: A comparison of coronary flow determined by the nitrous oxide method and by a direct method using the rotameter, Circulation **3**:89, 1951.
5. Lawther, P. J., and Bates, D. V.: A method for determination of nitrous oxide in blood, Clin. Sc. **12**:91, 1953.
6. Rowe, G. G.: The nitrous oxide method for determining coronary blood flow in man, Am. Heart J. **58**:268, 1959.
7. Bing, R. J.: Determination of coronary blood flow, Methods in Medical Research, Vol. 8, Chicago, 1960, Year Book Publishers, Inc., p. 269.
8. Forte, I., Williams, A. J., Schmitthenner, J. E., Neal, H., Woske, H., Richards, R., and Hafkenschiel, J. H.: Coronary blood flow using radioactive iodine compared with nitrous oxide, Fed. Proc. **19**:90, 1960.
9. Eckenhoff, J. E., Hafkenschiel, J. H., Harmel, M. H., Goodale, W. T., Lubin, M., Bing, R. J., and Kety, S. S.: Measurement of coronary blood flow by the nitrous oxide method, Am. J. Physiol. **152**:356, 1948.
10. Foltz, E. L., Page, R. G., Sheldon, W. F., Wong, S. K., Tuddenham, W. J., and Weiss, A. J.: Factors in variation and regulation of coronary blood flow in intact anesthetized dogs, Am. J. Physiol. **162**:521, 1950.
11. Goodale, W. T., and Hackel, D. B.: Measurement of coronary blood flow in dogs and man from rate of myocardial nitrous oxide desaturation, Circulation Res. **1**:502, 1953.
12. Forte, I., Williams, A. J., Potgieter, L., Schmitthenner, J. E., Hafkenschiel, J. H., and Riegel, C.: Coronary blood flow and cardiac oxygen metabolism during nicotine-induced increases in left ventricular work, Ann. New York Acad. Sc. **90**:174, 1960.
13. Forte, I. E., Potgieter, L., and Schmitthenner, J. E.: Effects of hypertensin on arterial pressure, heart work and cardiac oxygen utilization, Circulation Res. **8**:1218, 1960.
14. Hafkenschiel, J. H.: Determination of cerebral blood flow in man using an infrared analyzer to measure blood nitrous oxide, Fed. Proc. **14**:67, 1955.
15. Kennedy, C.: A micromethod for determination of nitrous oxide in blood, J. Appl. Physiol. **11**: 141, 1957.
16. Mainland, D.: The treatment of clinical and laboratory data, Edinburgh, 1938, Oliver and Boyd.
17. Sapirstein, L. A., and Ogden, E.: Theoretic limitations of the nitrous oxide method for the determination of regional blood flow, Circulation Res. **4**:245, 1956.
18. Bing, R. J., Hellems, H. K., and Regan, T. J.: Measurement of coronary blood flow in man, Circulation **22**:1, 1960.

Hemodynamic responses to administration of mephentermine in normotensive and hypotensive dogs

*A. W. Horsley, M.D.**
*John W. Eckstein, M.D.***
Iowa City, Iowa

Mephentermine sulfate† is used effectively in the treatment of hypotension.[1-3] There is confusion, however, concerning the mechanism by which the drug restores arterial pressure. In acute hypotension secondary to section of the spinal cord, sympathectomy, ganglionic blockade, and in the use of certain anesthetic agents, there may be loss of venomotor tone and pooling of blood in the periphery of the body.[4] This reduces venous return and leads to a fall in cardiac output. The decreased cardiac output rather than a loss of arteriolar tone appears to be the major cause of the hypotension.[5] It might be desirable to restore perfusion pressure in such cases by using a vasopressor drug which increases venous tone and cardiac output, rather than one which produces severe arteriolar constriction. Mephentermine is of interest because it has been reported by some[6,7] to have little effect on peripheral resistance.

Brofman and co-workers[3] found no change in cardiac output in dogs or man after the administration of mephentermine, even though arterial pressure increased. They attributed the increased pressure to increased peripheral resistance, Others[6,7] report that the drug has little effect on peripheral resistance, but that it increases the force of myocardial contraction. Because of these conflicting ideas, we reexamined the hemodynamic effects of mephentermine in dogs.

Methods

The experiments were done on intact mongrel dogs. The 6 animals in Group I were anesthetized lightly with thiopental sodium, treated with gallamine triethiodide,‡ intubated and ventilated with a fixed-volume respirator. End-expiratory concentration of carbon dioxide was monitored continuously with a Liston-Becker carbon-dioxide analyzer. Ventilation was adjusted initially so that end-expiratory concentration of carbon dioxide was about 4 per cent. Repeated doses of gallamine were given at 30-minute intervals in order to maintain relaxation of skeletal muscle. The dogs of Group II were prepared in the same way,

From the Hemodynamic Laboratory, Cardiovascular Research Laboratories, Department of Internal Medicine, State University of Iowa College of Medicine, Iowa City, Iowa.
Supported by Research Grant H-2644 from the United States Public Health Service, and aided by a grant from the Iowa Heart Association.
Received for publication June 10, 1960.
*Research Fellow of the American College of Physicians.
**Established Investigator of the American Heart Association.
†Wyamine, Wyeth Laboratories, Philadelphia, Pa.
‡Flaxedil, Lederle Laboratories, American Cyanamid Co., Pearl River, N.Y.

but, in addition, they were made hypotensive with intravenous injections of 100 mg. of hexamethonium. Three dogs in Group I were included in this group. They were made hypotensive after a 30-minute recovery period which followed the administration of mephentermine. The other 3 dogs were prepared as described, and ganglionic blockade was induced without prior administration of mephentermine. The dogs of Group III were anesthetized with intravenous pentobarbital sodium, 30 mg. per kilogram. These animals were not ventilated artificially. No effort was made to control their end-expiratory CO_2 tension or arterial oxygen saturation. The dogs of Group IV were the same animals used in Group III. Hexamethonium was administered to these after a 30-minute recovery period.

Two catheters were inserted through an external jugular vein. The tips were placed at the junction of the superior vena cava and right atrium. Needles were placed in the left carotid and femoral arteries and in the femoral vein. Cardiac output was measured by the indicator-dilution method with injections of indocyanine green dye into the right atrium. Dyed blood was drawn from a carotid artery through a Gilford densitometer, and time-concentration curves were recorded with a Sanborn direct-writing oscillograph. The blood was returned to the animal after each withdrawal by reversing the motor on the pump. Loss of blood was negligible except for the 50 ml. taken at the beginning of the experiment to calibrate the densitometer. Femoral arterial and right atrial pressures were recorded continuously by means of Statham strain gauges.

About one hour was required to set up the experiment after the animal was anesthetized. This was ample time for disappearance of the effects of thiopental in the animals of Groups I and II. Several dye curves were obtained during the next 15 to 30 minutes in order to establish control values. Mephentermine sulfate, 0.3 to 0.6 mg. per kilogram in 3 to 5 ml. of normal saline, was then injected into the femoral vein. Dye curves were obtained when arterial pressure became stable after having reached its maximal level. Curves were obtained in some animals at irregular intervals for 30 minutes after the injection of mephentermine.

Cardiac output was calculated according to the method of Hamilton.[8] Mean blood pressures were obtained by electrical integration of the output of the strain gauges. Peripheral resistance was determined by dividing the difference between mean arterial and right atrial pressures by cardiac output. The results are expressed in arbitrary units. Heart rate was determined by counting arterial pulses at the time of inscription of the dye curves. The data were analyzed according to methods described by Fisher.[9]

Results

The data from 22 experiments performed on 14 dogs are summarized in Table I. The data are grouped according to the control state of the animals. The responses to mephentermine in the different groups cannot be compared quantitatively, however, because of the differences in the dose of the drug.

An increase in arterial pressure was noted in each dog after rapid intravenous injection of the mephentermine. The increase appeared within 1 minute after the injection, and the peak response occurred in 2 to 4 minutes. The return of the pressure to control levels took place gradually over a period of 20 to 30 minutes. There was a tendency for mean right atrial pressure to increase in each group, but the changes were small and not considered to be significant.

Cardiac output increased in each of the 22 experiments regardless of the control state of the animal before the administration of mephentermine. In 8 dogs the cardiac output was measured 1 minute after the injection. It was found to be unchanged in 5 of them even though arterial pressure had increased appreciably in all 8. This observation suggests that the drug causes an increase in arteriolar tone before the heart increases its output. The increased output appeared soon after the initial increase in arteriolar tone and persisted for about 30 minutes. The stroke volume increased in 20 of the 22 experiments. The relatively low control values in Groups I and II may be attributed to the tachycardia secondary to the selective vagolytic action of the gallamine. Changes in heart rate were

Table I. Hemodynamic responses to the administration of mephentermine

Dog number	Dog weight (Kg.)	Dose (mg./Kg.)	Mean arterial pressure (mm. Hg)		Mean right atrial pressure (mm. Hg)		Cardiac output (ml./min.)		Stroke volume (ml.)		Heart rate (beats/min.)		Peripheral resistance (units)	
			Before	*After*	*Before*	*After*	*Before*	*After*	*Before*	*After*	*Before*	*After*	*Before*	*After*
Group I														
1	15.3	0.49	140	230	8.5	8.8	1,794	2,328	9.3	12.9	192	180	78.0	98.8
2	14.5	0.52	130	160	7.5	8.2	2,856	3,168	16.6	22.0	186	144	45.5	50.5
3	19.1	0.39	127	185	4.8	5.0	1,452	1,800	6.7	13.0	216	138	87.5	102.8
4	10.5	0.34	130	175	5.4	4.7	1,890	2,166	8.3	8.8	228	246	68.8	80.8
5	18.7	0.40	117	240	9.5	10.7	3,768	4,482	16.1	20.0	234	220	31.1	53.5
6	20.5	0.30	130	175	7.2	8.2	2,766	3,444	15.4	22.0	180	156	47.0	50.8
Mean	16.4	0.41	129	194	7.2	7.6	2,421	2,898	12.1	16.5	206	181	59.7	72.9
Standard error of mean difference			14.2		0.28		78.0		0.92		13.2		3.19	
Probability			< 0.01		< 0.2		< 0.01		< 0.01		< 0.2		< 0.01	
Group II														
2	14.5	0.52	105	135	7.5	7.5	1,908	2,736	9.9	13.0	192	210	55.0	49.3
4	10.5	0.34	100	178	5.0	4.8	1,380	1,854	6.2	7.9	222	234	72.5	96.0
5	18.7	0.40	122	230	8.5	8.8	2,256	3,246	10.2	12.9	222	252	54.1	70.9
7	15.5	0.48	125	240	5.0	5.0	1,160	1,254	6.4	5.3	180	234	107.8	191.4
8	16.5	0.45	60	250	4.7	7.6	954	1,554	6.9	9.6	138	162	62.9	160.9
9	26.5	0.28	120	310	2.0	2.6	3,138	4,146	19.4	19.2	162	216	38.2	74.8
Mean	17.0	0.41	105	224	5.5	6.1	1,799	2,465	9.8	11.3	186	218	65.1	107.2
Standard error of mean difference			25.7		0.47		143.0		0.71		7.4		16.46	
Probability			< 0.01		< 0.3		< 0.01		< 0.1		< 0.01		< 0.05	

Group III														
10	16.4	0.46	148	200	5.0	5.7	2,604	3,252	16.7	18.7	156	174	56.8	61.5
11	21.5	0.30	133	150	5.0	6.0	2,022	2,778	14.0	20.1	150	138	65.8	54.0
12	19.3	0.30	140	170	8.0	7.8	2,094	2,742	15.9	21.8	132	126	66.9	62.0
13	22.5	0.30	100	150	8.0	7.0	2,582	4,872	33.2	36.9	108	132	38.7	30.8
14	17.5	0.30	100	143	5.7	5.5	2,034	2,754	14.7	15.8	138	174	49.2	51.9
Mean	19.4	0.33	124	163	6.3	6.4	2,467	3,280	18.9	22.7	137	149	55.5	52.0
Standard error of mean difference			6.6		0.36		121.0		1.0		9.1		2.82	
Probability			< 0.01		< 0.5		< 0.01		< 0.02		< 0.3		< 0.4	
Group IV														
10	16.4	0.30	105	150	4.6	4.9	1,998	2,238	10.1	11.3	198	234	52.6	67.0
11	21.5	0.30	120	200	6.5	6.0	2,442	3,288	13.6	26.2	180	108	49.1	60.8
12	19.3	0.30	125	200	5.5	6.0	2,730	3,174	15.2	24.5	180	102	45.8	63.0
13	22.5	0.30	88	137	4.7	3.9	4,092	5,250	27.3	28.2	150	186	21.5	26.1
14	17.5	0.30	105	165	5.0	6.7	2,508	3,018	15.2	16.2	165	186	41.9	54.7
Mean	19.4	0.30	109	170	5.3	5.5	2,754	3,394	16.3	21.3	175	163	42.2	54.3
Standard error of mean difference			6.9		0.44		162.0		2.5		26.1		2.10	
Probability			< 0.001		< 0.7		< 0.02		< 0.2		< 0.7		< 0.01	

Group I: Treated with gallamine. No ganglionic blockade.
Group II: Treated with gallamine. Ganglionic blockade with hexamethonium.
Group III: Anesthetized with pentobarbital sodium. No ganglionic blockade.
Group IV: Anesthetized with pentobarbital sodium. Ganglionic blockade with hexamethonium.

variable and not significant in most groups.

Calculated peripheral resistance increased in 18 of the 22 experiments.

Discussion

Mephentermine has been reported to increase the force of myocardial contraction.[6,10,11] Recent evidence indicates that this is an indirect effect produced by the release of catecholamines.[12] We found that the drug causes peripheral venous constriction and a shift of blood from the peripheral vessels in man.[13] If it causes blood to be "pushed" centrally, and if it also increases the force of myocardial contraction, it might be expected to increase cardiac output. An increased output was observed regularly in these experiments.

The increase in peripheral resistance seen in most of the dogs indicates that mephentermine caused a decrease in the caliber of the arterioles. A decrease in caliber in the face of an increase in arteriolar distending pressure and blood flow could be caused only by an increase in arteriolar tone. We cannot evaluate the degree of increased arteriolar tone from these studies, but Borden and Haddy[14] found that mephentermine caused less arteriolar constriction in the forelimb of dogs than did norepinephrine or metaraminol. Regardless of the magnitude of the arteriolar response it appears that mephentermine may elevate arterial pressure by increasing both cardiac output and peripheral resistance.

Summary

The hemodynamic responses to mephentermine were studied in dogs anesthetized with pentobarbital and in those treated with gallamine. Observations were made in normotensive animals and in animals made hypotensive by intravenous hexamethonium.

Mephentermine regularly caused an increase in cardiac output and arterial pressure regardless of the control state of the animal. Calculated peripheral resistance increased in 18 of the 22 experiments.

In this study, mephentermine raised the level of arterial pressure by increasing both cardiac output and peripheral resistance.

REFERENCES

1. Hellerstein, H. K., Brofman, B. L., and Caskey, W. H.: Shock accompanying myocardial infarction: treatment with pressor amines, AM. HEART J. **44**:407, 1952.
2. Blundell, A. E., Pillon, J. W., and Ansbro, F. P.: Mephentermine—a clinically useful and effective pressor amine, Anesth. & Analg. **35**:483, 1956.
3. Brofman, B. L., Hellerstein, H. K., and Caskey, W. H.: Mephentermine—an effective pressor amine, AM. HEART J. **44**:396, 1952.
4. Weil, M. H.: Current concepts on the management of shock, Circulation **16**:1097, 1957.
5. Smith, J. R., and Hoobler, S. W.: Acute and chronic cardiovascular effects of pentolinium in hypertensive patients, Circulation **14**:1061, 1956.
6. Welch, G. H., Braunwald, E., Case, R. B., and Sarnoff, S. J.: The effect of mephentermine sulfate on myocardial oxygen consumption, myocardial efficiency and peripheral vascular resistance, Am. J. Med. **24**:871, 1958.
7. Aviado, D. M., Jr.: Cardiovascular effects of some commonly used pressor amines, Anesthesiology **20**:71, 1959.
8. Hamilton, W. F., Moore, J. W., Kinsman, J. M., and Spurling, R. G.: Studies on the circulation. IV. Further analysis of the injection method and of changes in hemodynamics under physiological conditions, Am. J. Physiol. **99**:534, 1932.
9. Fisher, R. A.: Statistical methods for research workers, ed. 10, Edinburgh, 1946, Oliver and Boyd, Ltd.
10. Gazes, P. C., Goldberg, L. I., and Darby, T. D.: Heart force effects of sympathomimetic amines as a basis for their use in shock accompanying myocardial infarction, Circulation **8**:883, 1953.
11. Goldberg, L. I., Cotten, M., Darby, T. D., and Howell, E. V.: Comparative heart contractile force effects of equipressor doses of several sympathomimetic amines, J. Pharmacol. & Exper. Therap. **108**:177, 1953.
12. Swaine, C. R., Perlmutter, J., and Ellis, S.: Mechanism of action of mephentermine, Fed. Proc. **19**:122, 1960.
13. Horsley, A. W., and Eckstein, J. W.: The effect of mephentermine on peripheral venous tone, Clin. Res. **7**:238, 1959.
14. Borden, C., and Haddy, F. J.: A comparison of the peripheral vascular effects of certain sympathomimetic amines, Clin. Res. **7**:237, 1959.

Salvage of heart muscle by fibrinolytic therapy after experimental coronary occlusion

Irwin Nydick, M.D.
Paul Ruegsegger, M.D.
Claude Bouvier, M.D.
Robert V. Hutter, M.D.
Ramon Abarquez, M.D.
Eugene E. Cliffton, M.D.
John S. LaDue, M.D., Ph.D.
New York, N. Y.

Fibrinolytic therapy has been used for the lysis of large thrombi of arterial or venous origin in many experimental and clinical situations, including myocardial infarction in man. This type of therapy of coronary occlusion and myocardial infarction seems logical, but two serious theoretical objections must be considered. First, even under ideal circumstances an average of 3 to 6 hours is necessary for the lysis of thrombi,[7,9] a period considered to be too long to protect against the tissue breakdown which is said to be inevitable after myocardial ischemia of only 30 to 45 minutes' duration.[1,2] Second, in at least 40 per cent of the patients who die of "coronary thrombosis and myocardial infarction," fresh coronary thrombi cannot be demonstrated at autopsy,[10] and there would thus be no obvious therapeutic target for clot-dissolving agents.

The evidence for such short-lived myocardial viability is based upon many studies in which no attempts had been made to alter either the coagulability of the myocardial blood supply or the metabolic state of the myocardium during this period of deprivation. Necrosis appeared to be inevitable after ischemia in excess of 30 minutes in these studies.

The myocardium may resist anoxia for more than 2 hours without irreversible effects on its function when the coronary system is perfused with heparin or during hypothermia.[3,4] Myocardial excitability, energy production, and energy utilization deteriorate at different rates during anoxia, indicating gradations of resistance of biochemical and biophysical processes of the heart to ischemia.[5] An isolated myocardial fiber can continue to utilize nutriment, contract and relax, and perform work after 6 months in proper nutrient media.[6] These are but a few of the factors that must be studied before we can define the final limits of myocardial viability. The heart may actually function under conditions previously considered inimical to its integrity.

From the Sloan-Kettering Division of Cornell University Medical College, and the Departments of Medicine and Surgery, Memorial Center for Cancer and Allied Diseases, New York, N. Y., and the Andre & Bella Meyers Laboratory of the Sloan-Kettering Institute, New York, N. Y.
This work was supported by Grants Nos. H1978 and H2867 of the National Institutes of Health, Bethesda, Md.
Received for publication June 16, 1960.

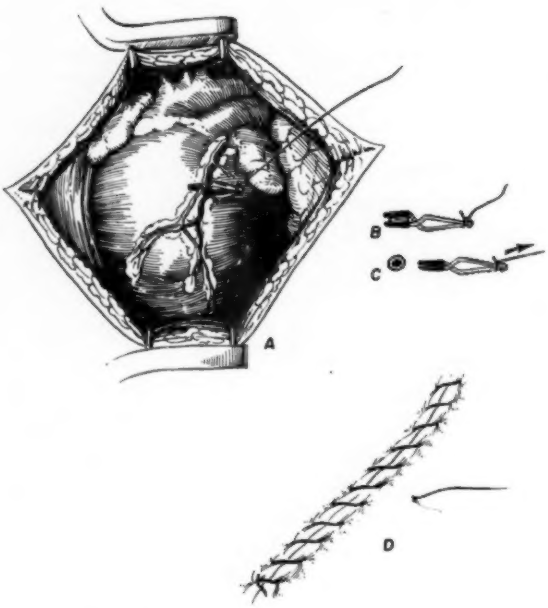

Fig. *1*. Technique of temporary coronary artery occlusion.

In our previous experiments, we noted a profound alteration in the early micropathology of the heart after fibrinolytic treatment of experimental coronary thrombi.[7] The large thrombi in the major coronary artery were consistently lysed. At the same time, minute fibrin thrombi in the microcirculation (arterioles, capillaries, and venules), and interstitial collections of edematous fluid which apparently was rich in protein were noted in the control dog hearts but were absent in the fibrinolytic-treated animals. Deposition of epicardial fibrin and vascular congestion were also significantly reduced in fibrinolytic-treated dogs. We postulated that this "microblockade" during initial phases of infarction might contribute to the "irreversible" damage of these marginal zones, and that the fibrinolytic dissolution of this blockade could salvage these areas. We felt that it was necessary to determine whether this fibrinolytic treatment could extend the viability of the myocardium for prolonged periods of time.

The present series of experiments was designed to study whether fibrinolytic enzymes could exert an important effect upon myocardial viability apart from their gross clot-dissolving action as suggested by our previous study. Infarcts were produced as uniformly as possible by occluding the left anterior coronary artery immediately distal to its first side branch for a standard period of time and assessing the end result of enzyme treatment by comparing the size and structure of infarcts in a treated and a control group. Extension of viability would thus be reflected in a reduction in the size of infarcts, whereas deleterious effects should be manifested by larger areas of necrosis. The structural alterations were analyzed in finer detail by microscopic study.

Methods

Mongrel dogs were anesthetized with intravenous sodium pentobarbital, and intubated. Artificial respiration was maintained with ambient air through a Harvard respirator. Under aseptic technique the thorax was entered through the fourth left intercostal space. The left anterior descending coronary artery was dissected and then occluded by a vascular clamp immediately below its first side branch. (The anatomy of this region was remarkably constant, allowing consistent levels of ligation.) Braided No. O silk or monofilament nylon string was tied to the clamp and led through a distant intercostal space through the chest wall. The chest was then closed. After 3 hours the string was firmly pulled taut, removing the occluding clamp from the artery (Fig. 1).

The animals were divided into control and treated groups at random. In the treated group a continuous infusion of fibrinolysin* was initiated 2 hours after coronary artery occlusion and continued for a total of 5 hours (1 hour before, and 4 hours after, removal of the clamp). In all animals, specimens of blood were tested for fibrinolytic activity by the euglobulin method[8] before operation, at the time of removal of the clamp, during and at the termination of the infusion, and then daily until autopsy.

The dogs were autopsied at intervals up to 21 days. Before autopsy they were hepar-

*Mixture of crude human plasminogen (Merck, Sharp & Dohme, Lot No. 1108-86N), 10,000 Christensen units per hour after activation by streptokinase, and of crude human plasminogen (Ortho), 80,000 units per hour after activation with Varidase (Lederle—streptokinase and streptodornase), 2,500 units per hour. Theoretically, this mixture produced varying fibrinolytic and proteolytic activity due to the formation of plasminogen-activator, human plasmin and canine plasmin of intense degree.

inized and sacrificed by the injection of 20 to 50 c.c. of sodium pentobarbital intravenously. The hearts were removed gently so as not to dislodge any thrombi, and the position of the vascular clamp was identified within the chest. The coronary arteries were then carefully dissected and opened to verify their patency. The hearts were finally transected serially from base to apex at intervals of 1 cm., starting immediately below the site of previous coronary artery occlusion. The areas of infarction were identified in the gross, fresh specimens and measured in each transection of the specimen as accurately as possible. Histologic

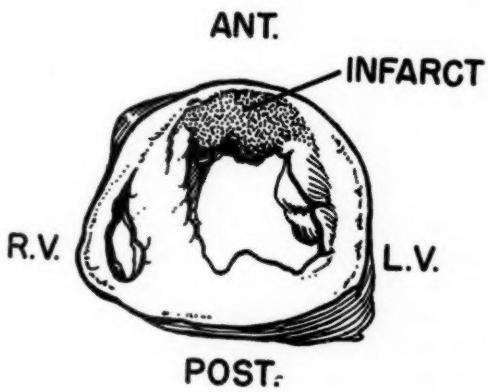

Fig. *2*. Transverse section of entire heart, illustrating region of infarction.

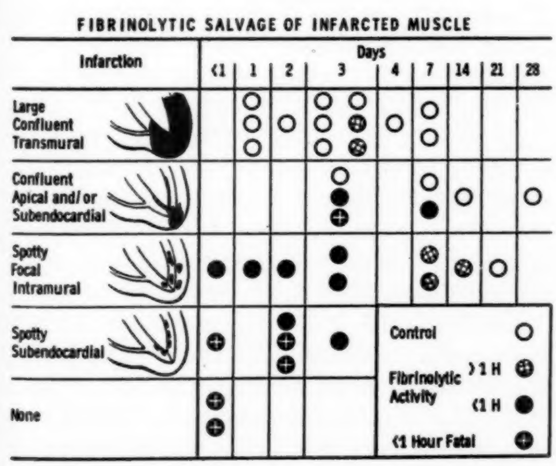

Fig. *3*. Gross extent of myocardial infarction. Open circles = controls; solid circles = treated animals, euglobulin lysis times shorter than 1 hour; shaded circles = treated animals, euglobulin lysis times 1 to 2 hours; and solid circles with crosses = treated animals, hemorrhagic death. Note the preponderance in the control animals of infarction in the large, confluent, transmural group, contrasted with the infarcts in more distal and subendocardial regions in the treated animals.

sections were obtained from the central and marginal zones of the infarcted area and the presumably normal posterior wall of the left ventricle at the same level of transection (Fig. 2). One of us (C.B.) analyzed all histologic sections in detail without knowledge of whether the animal had received treatment.

Results

Fifty-two animals were operated upon. Ten were eliminated because they died acutely within ½ hour after occlusion with the clamp still in place and thus could not be regarded either as control or treated animals. Evaluation of the experimental data demonstrated that the therapeutic effect was closely related to the circulating fibrinolytic activity. The degree of fibrinolytic activity in the treated group of 26 animals showed a marked variation despite constancy of dosage and duration of plasmin treatment. The fibrinolytic activity (lysis time of a standard fibrin clot) was less than 1 hour in 15, 1 to 2 hours in 5, and more than 2 hours in 6 animals. All 16 control animals showed lysis times of more than 5 hours, i.e., little evidence of spontaneous lysis. Infarcts equal in size to those of the control animals were seen in all of the 6 animals in which the lysis times were longer than 2 hours.

This variability of response of the euglobulin lysis time to the standard dose of fibrinolysin was expected, since no consideration was made of variations in the weights of the dogs, the levels of circulating inhibitor, etc. In subsequent experiments, we are now employing a modification, an in vitro dose prediction method,[12] and are able to accurately produce consistent levels of circulating fibrinolytic activity.

Gross extent of infarction. Fig. 3 demonstrates the diminution in extent of myocardial infarction after fibrinolytic therapy. A significant alteration in location of the infarcts is seen: the areas of infarction in the treated animals tending to be spotty. located in the more distal apical portions, and subendocardial rather than large, confluent, and transmural. Eleven of 16 control animals showed extensive confluent transmural infarcts. Somewhat smaller infarcts in 4 of the other animals were in

Fig. 4A. Large, confluent, transmural infarction (control).

infarcts that were 7 days old or older, a length of time in which shrinkage from the contraction of fibrous replacement tissue would be expected.

Those animals in which the lysis times were 1 hour or less had the smallest infarcts. The extent of infarction in animals in which the lysis times were between 1 and 2 hours was intermediate between that in the control and that in the "ideally" treated groups.

Six treated animals died from extensive hemorrhage into the chest (black circles with white crosses in Fig. 3), 3 within 12 to 24 hours, 2 within 48 hours, and 1 in 72 hours. The 3 animals which died within 12 hours do not constitute a valid group for determining gross extent of infarction since such early infarction does not lend itself to accurate measurement. These treated animals died from an oozing into the chest cavity from the surgical wound as a result of the treatment.

This increased mortality was not unexpected in the treated group despite meticulous attempts at hemostasis, but was not due to infarction per se and fortunately would find no analogy in a clinical situation. Many animals were rendered afibrinogenemic as a result of the intense induced fibrinolysis and proteolysis.

Fig. 4*A* shows a typical large, confluent, transmural infarct in a control animal 3 days old, and this is in contrast to a small, spotty, subendocardial infarct in a treated animal, shown in Fig. 4*B*. At the time of release of the clamp the euglobulin lysis time was 26 minutes in the treated animal. This diminution in the size of the infarct was the most favorable result in the treated group.

The typical microscopic findings in an untreated heart are seen in Figs. 5*A* and 5*B*. Fibrin thrombi in minute vessels, confluent necrosis of the myocardium, and interstitial protein-rich edema are evident. In contrast, Figs. 6*A* and 6*B* demonstrate the pattern in a treated animal. Microthrombi are absent, the myocardial damage is focal rather than confluent, and there is negligible interstitial edema. Myocardial rupture did not occur as a result of fibrinolytic therapy, nor was there an increased incidence of intramyocardial hemorrhage in the treated group. In addition, no other deleterious effects of the proteolytic enzyme were noted upon the uninfarcted posterior myocardial wall of these animals.[11]

Tables I and II enumerate the incidence of microthrombi or blockade of small vessels by fibrin-like material, and the character of the myocardial damage in the treated and untreated dogs. Ten of 13 control animals demonstrate microthrombi, whereas microthrombi were noted in only 2 of 15 adequately treated animals. The microthrombi noted in one of the animals which had been treated for 3 days were probably present as part of an unrelated arteriolar disease antedating the treatment of this animal, since they appeared to be older than 3 days by microscopic criteria.

Table I. *Incidence of thrombi in microcirculation in treated group with euglobulin lysis times shorter than 1 hour*

Infarct age	*Controls*	*Treated*
12–24 hr.	3/3	0/5
48 hr.	1/2	1/4
3 days	4/5	1/5*
4–7 days	2/3	0/1
Total	10/13	2/15

*Older than 3 days.

Table II. *Incidence of type of necrosis in treated group with euglobulin lysis times shorter than 1 hour*

Infarct age	*Controls*		*Treated*	
	Confluent	*Focal*	*Confluent*	*Focal*
12–24 hr.	3	–	1	4
48 hr.	2	–	1	3
3 days	4	1	–	5
4–7 days	2	1	–	1
Total	11	2	2	13

Eleven of 13 control animals revealed only confluent necrosis, whereas focal necrosis was present in 13 of the treated group, and confluent necrosis alone in only 2 of these dogs. This low incidence of microthrombi and confluent necrosis in the treated animals is statistically significant.

Discussion

After coronary occlusion there are extensive zones of starved myocardium surrounding areas which are irreversibly damaged. Fibrinolytic therapy is one means of alleviating this starvation and returning portions of these marginal zones to anatomic and functional integrity. The collateral blood supply probably plays a vital role in maintaining some nourishment at first, and the intrinsic resistance of portions of the myocardial fiber to severe injury appears to be much greater than previously estimated.

These studies indicate that there are large areas of myocardium that can be salvaged up to 3 hours after ischemic injury. The apical and subendocardial regions appear to be most irreversibly damaged, whereas the marginal areas are salvable for long periods by fibrinolytic therapy. Our results show that these zones of reversible injury may constitute 25 to 50 per cent of the area of infarction expected in control animals. This apparent extension of the limits of myocardial viability, previously not observed after restoration of the blood supply alone, appears to be the direct effect of fibrinolytic activity upon the acute ischemic tissue reaction in the heart muscle, and demonstrates that the speed of muscle breakdown within an infarct area is not uniform. In our studies, we were impressed with the powerful influence of these enzymes upon the tissue reaction. It appears logical that the use of these "clot dissolvers" for the lysis of major clots is not possible without profound effects at the tissue level wherever fibrin may be deposited. There is an obvious need to extend the study of these enzymes to any tissue reaction associated with deposition of fibrin

We interpret the absence of microthrombi and interstitial precipitation of

Fig. *4B*. Spotty, focal, subendocardial infarction (treated).

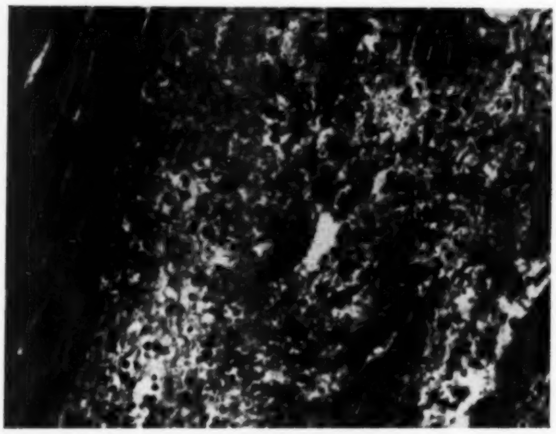

Fig. *5A*. Seven days, control. Dense mesh of interstitial fibrin and coagulated protein in infarcted zone. There are necrotic polymorphonuclear leukocytes and macrophages in the coagulum.

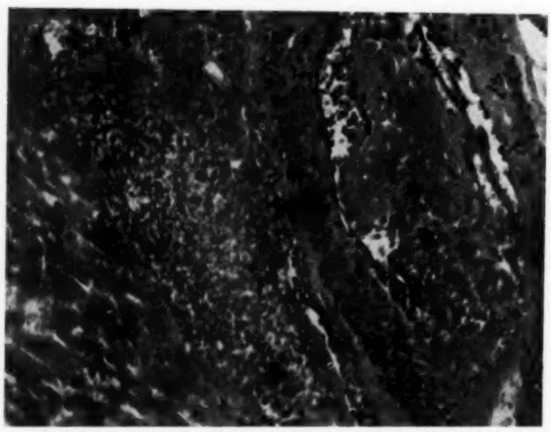

Fig. *5B*. Seven days, control. Note arteriole with organizing thrombus (*right*). Adjacent to the arteriole is a large zone of interstitial fibrin and protein coagulum which contains necrotic exudate. There are infarcted muscle fibers which are anuclear and fragmented (*left lower*).

protein-rich edema in the hearts of treated animals, in contrast to the findings in the hearts of control animals, as evidence that nutrition is restored to the marginal muscle regions by maintenance of the patency of the capillary circulation and clogged tissue spaces. Since all animals were heparinized before they were sacrificed, these findings cannot be due to postmortem clotting. Furthermore, the high incidence of small focal areas of necrosis in the treated animals rather than large confluent zones indicates that reversible local changes are present, such as those often seen in patients with long-standing angina pectoris, rather than irreversible massive generalized deprivation. We had previously postulated[7] that fibrinolytic therapy dissolved out the microblockage to the coronary circulation. However, analysis of the microscopic findings in a control group of dogs which died within 12 hours after infarction failed to reveal the presence of microthrombi before 6 hours. Thus, fibrinolytic therapy may have *prevented* this blockade rather than reversed it. Whether it is necessary to render these animals hypo- or afibrinogenemic to accomplish this beneficial effect, or whether some other less specific mechanism of action is important is presently under study in our laboratory.

It is certain that this hypothesis of microthrombosis is an oversimplification of the many factors which govern the rate of myocardial death. The small number of microthrombi we have seen in each heart is quantitatively insufficient to explain the degree of blockade of the microcirculation which we have postulated. However, it is possible that these microthrombi are the expression of the end result of hypercoagulability after ischemic injury, and that *functional* capillary blockade occurs even prior to actual formation of microthrombi. At present, we are measuring the coagulability of the coronary venous blood after coronary occlusion, and preliminary data indicate that a state of hypercoagulability is produced within 1 hour after ischemia of the myocardium. This state can serve to perpetuate deprivation of cell nutriment at a microscopic level.

These experimental results encourage the use of fibrinolytic therapy in human myocardial infarction. Successful therapy within the previously accepted limits of myocardial viability of ½ hour after total ischemia is impractical if not totally impossible, especially if the only aim is to disso ve an obstructing coronary thrombus. It seems unlikely that total dissolution of this thrombus could be affected in less than 8 hours from the time of its formation, even under optimal circumstances under clinical conditions. This estimate of elapsed time includes inevitable delays in the obtaining of medical assistance, transportation to the hospital, organization of the treatment personnel, etc., as well as an estimated 4 to 6 hours necessary for actual clot lysis.[9,13]

On the other hand, the goal of restoration of the patency of the capillary circulation more quickly after myocardial infarction is logical and feasible. It seems likely that these enzymes may reach marginal zones of ischemic myocardium through collaterals before the major coronary channel is reopened. That this goal may be of the utmost importance is further emphasized by the recent evidence that fresh *major* coronary thrombi are found in less than 60 per cent of the cases of sudden cardiac death.[10]

A further drawback to clinical effectiveness may be our evidence that euglobulin lysis times of less than 1 hour seem to offer

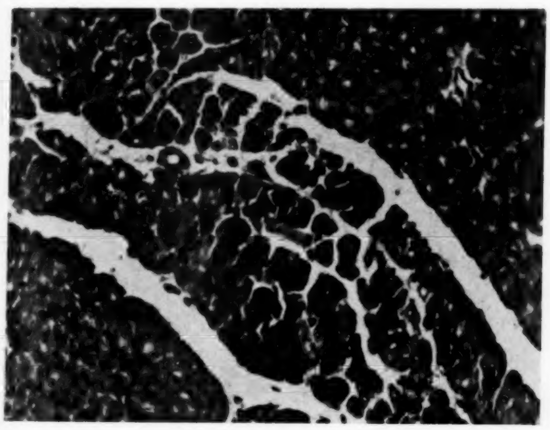

Fig. *6A*. Forty-eight hours, treated. Note isolated infarcted muscle fibers in center of photograph. They are darker, glossy, and anuclear. Note also clean interstitial space with no fibrin or protein debris.

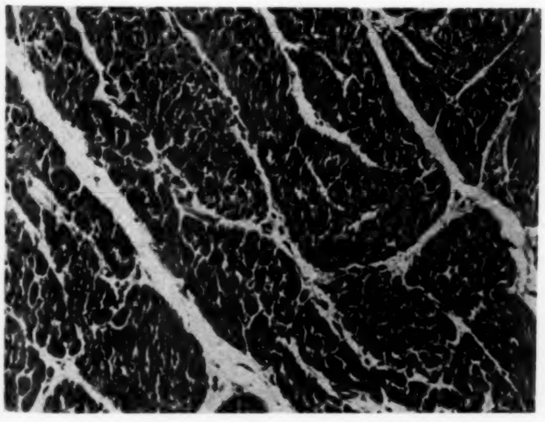

Fig. *6B*. Three days, treated. Note two infarcted muscle fascicles which are beginning to organize. The remaining muscle fascicles are normal; the interstitial spaces are clean. This reaction is probably the result of focal starvation of temporary nature.

optimal diminution in the size of the infarct. This intense fibrinolytic activity over a period of 6 to 12 hours may cause hemorrhagic complications with significant depletion of circulating fibrinogen and other clotting factors. Since the proportions of fibrinolysin and streptokinase utilized in this study obviously produced circulating and tissue fibrinolysis and proteolysis of intense degree, but in a proportion peculiar to these particular mixtures, other types of fibrinolytically active states may produce results in the myocardium which are different from those reported here.

There was no evidence that the fibrinolytic therapy itself in the present experiments caused myocardial hemorrhage, rupture, or rheumatic-like or degenerative lesions as reported with papain or streptococcal proteinase in rabbits.[11]

Summary

1. The extent of experimental canine myocardial infarction was markedly diminished by fibrinolytic therapy.

2. This effect appeared to be the result of maintaining the patency of the microcirculation of the heart, with the salvage of ischemic marginal areas after coronary occlusion.

3. Fibrinolytic therapy extends the duration of viability of large areas of the myocardium after ischemic injury.

4. Intense fibrinolytic activity was induced to the extent of producing hemorrhagic complications in some of the animals.

5. The implications of this therapy in human myocardial infarction are discussed.

REFERENCES

1. Blumgart, H. L., Gilligan, D. R., and Schlesinger, M. S.: Experimental studies on the effect of temporary occlusion of coronary arteries, AM. HEART J. **22**:374, 1941.
2. Tennant, R., Grayzel, D. M., Sutherland, F. A., and Stringer, S. W.: Studies on experimental coronary ligation, AM. HEART J. **12**:168, 1936.
3. Niazi, S. A., and Lewis, F. J.: Profound hypothermia in the monkey, with recovery after long periods of cardiac standstill, J. Appl. Physiol. **10**:137, 1957.
4. Webb, W. R., and Howard, H. S.: Extension of the limits of cardiac viability with total coronary occlusion, Surgery **42**:92, 1957.
5. Kardesch, M., Hogancamp, D. E., and Bing, R. J.: The survival of excitability, energy

production, and energy utilization of the heart, Circulation **18**:935, 1958.
6. Benson, E. S., Halloway, B. E., and Turbak, C. E.: Contractile properties of glycerol-extracted muscle bundles from the chronically failing canine heart, Circulation Res. **6**:122, 1958.
7. Ruegsegger, P., Nydick, I., Hutter, R. C., Freiman, A., Bang, N. U., Cliffton, E. E., and LaDue, J.: Fibrinolytic (plasmin) therapy of experimental coronary thrombi with alteration of the evolution of myocardial infarction, Circulation **19**:7, 1959.
8. Cliffton, E. E., and Cannamela, D. A.: Fibrinolytic and proteolytic activity of a human plasminogen prepared from fraction III of human plasma, J. Appl. Physiol. **6**:42, 1953.
9. Freiman, A. H., Bang, N. U., and Cliffton, E. E.: Studies on the production of intravascular thrombi and their treatment with fibrinolysin, Circulation Res. **8**:409, 1960.
10. Weinberg, A.: Personal communication.
11. Kellner, A., and Robertson, T.: Myocardial necrosis produced in animals by means of crystalline streptococcal proteinase, J. Exper. Med. **99**:495, 1954.
12. Sherry, S., and Alkjaersig, N.: Biochemical, experimental, and clinical studies of proteolytic enzymes; with particular reference to the fibrinolytic enzyme of human plasma, Ann. New York Acad. Sc. **68**:52, 1957.
13. Nydick, I., Ruegsegger, P., Abarquez, R., Cliffton, E. E., and LaDue, J. S.: The effect of fibrinolytic agents on myocardial infarction, Prog. Cardiovas. Dis. **3**:13, 1960.

The influence of high altitudes on the electrical activity of the heart

Electrocardiographic and vectorcardiographic observations in adolescence and adulthood

Dante Peñaloza, M.D.
Raúl Gamboa, M.D.
Emilio Marticorena, M.D.
Max Echevarría, M.D.
Juan Dyer, M.D.
Edilberto Gutierrez, M.D.
Lima, Peru

That right ventricular preponderance is a frequent electrocardiographic finding among healthy residents of high altitudes was first observed in Bolivia by Capdehourat.[1] Rotta[2] found signs of right ventricular hypertrophy and right bundle branch block in the native residents of high altitudes of Peru. Cosío and Corigliano[3] studied at sea level subjects who came from high altitudes and confirmed the above-mentioned findings. The electrocardiograms observed in the adult residents of high altitudes were classified by Rotta and Lopez[4] into four groups, similar to those described by Taquini[5] in chronic pulmonary heart disease. The present work has been carried out in order to investigate the genesis of such variable electrocardiograms. It complements a previous study made in children.[6]

It should be remembered that a moderate arterial oxygen unsaturation, polycythemia, increased pulmonary blood volume, and mild pulmonary hypertension are common findings in healthy people who live permanently at high altitudes.[7-11] These findings are physiologic characteristics in such a low pO_2 environment. Adaptive mechanisms in pulmonary function, blood chemistry, and enzymatic activity are also present in the residents of high altitudes who are capable of efficiently performing heavy exercise.[12,13]

Material and methods

Three hundred normal subjects were studied in Lima, at sea level, and 250 in Morococha, 14,900 feet (4,540 meters) above sea level. The individuals were distributed in three age groups: 15 to 20 years (100 subjects at sea level and 50 at high altitudes), 21 to 40 years (100 subjects at both levels), and 41 to 60 years (100 subjects at both levels). Male and female subjects in equal proportion were included in each age group. The residents of high

From the Department of Pathologic Physiology, and the Heart Laboratory of the Institute of Andean Biology, University of San Marcos, Faculty of Medicine, Lima, Peru.
This work was supported mainly by the School of Aviation Medicine, U.S.A.F., Randolph Field, Tex., Contract AF 41(657)249, and in part by the Special Research Fund of the Faculty of Medicine, Lima, Peru.
Received for publication April 11, 1960.

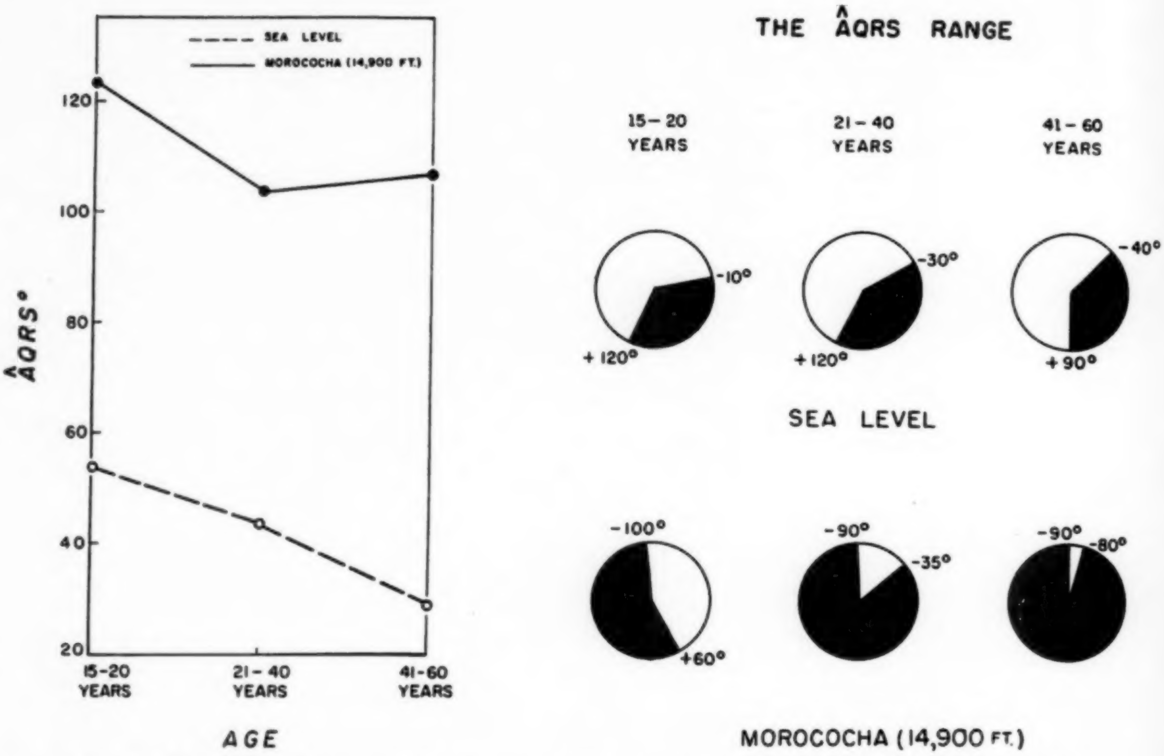

Fig. *1*. A right ÂQRS deviation is a common finding in healthy people who live permanently at high altitudes (*left*). As their age increases, the ÂQRS range is wider at high altitudes, and in older adults, ÂQRS can be found in any one of the Bayley sextants (*right*).

altitudes had lived 5 years without interruption in Morococha and had always lived at altitudes above 10,000 feet.

A Sanborn Viso-Cardiette, Model 52, electrocardiograph was used. Conventional leads and additional chest leads were taken in each subject. The vectorcardiograms were recorded according to Grishman's cube method[14] based on a modification of the trirectangular trihedron of Duchosal and Sulzer.[15] A Sanborn Vector Amplifier, Model 185, coupled to a Sanborn Viso-Scope, Model 169A, and a Polaroid Fairchild camera, Model F-296A, were employed. The vector loop was interrupted 400 times per second by intensity modulations.

Results

Ventricular activation process.

STATISTICAL ANALYSIS. Tables I, II, and III show the statistical analysis of the data concerning the ventricular activation process at sea level and at high altitudes. The difference between the mean values of ÂQRS obtained at sea level and those at high altitudes was statistically significant ($p < 0.001$) in all age groups (Table I), showing a right ÂQRS deviation at high altitudes (Fig. 1, *left*). However, as the age of the subjects increased, the ÂQRS range was wider at high altitudes, and in older adults the ÂQRS was in any one of the Bayley sextants (Fig. 1, *right*). Table II shows the voltage of the late R wave in Lead aV_R, and the R'/Q or S ratio in the same lead. The mean values at high altitudes were greater than, and showed a statistically significant difference from, those at sea level. Table III shows the voltage of the R wave and the $R/R + S$ ratio in Lead V_1. The mean values were significantly greater at high altitudes in the adolescent group only. At high altitudes the values for the R/S ratio in Lead V_5 were lower, and the index R in Lead V_1 + S in Lead V_5 showed higher values. The difference between the mean values obtained in the two places studied is highly significant in all age groups.

ELECTROCARDIOGRAPHIC AND VECTORCARDIOGRAPHIC PATTERNS. In adult dwellers of high altitudes there was a wide range in SÂQRS direction, the configura-

tion of the QRS complex was highly variable both in the limb and precordial leads, and the two-dimensional projections of the spatial QRS loop showed wide diversity. In order to systematize our results, we will describe five principal patterns according to the spatial SÂQRS orientation. In this way we do not prejudge differences in the ventricular activation process.

1. SÂQRS in the right inferior posterior octant. SÂQRS was directed to the right, inferiorly, and somewhat posteriorly in most of the adult inhabitants of high altitudes (38.4 per cent). This SÂQRS position was a vectorial resultant of two portions differently oriented but approximately similar in magnitude (Fig. 2). The mid QRS vectors (QRS loop 2 or "left ventricular" vectors[16]) were directed to the left, downward, and somewhat anteriorly. The late QRS vectors (QRS loop 3 or "basal" vectors[16]) were large and pointed to the right, upward, and posteriorly. The former showed their major projection on the frontal and horizontal planes, and the latter on the sagittal view. The early QRS vectors (QRS loop 1 or "septal" vectors[16]) were small and anteriorly oriented, whether to the left or to the right. The frontal QRS loop was wide and showed a clockwise rotation. The horizontal QRS loop was narrow and approximately perpendicular to the axis of Lead V_1, and it was inscribed in a clockwise direction or in a figure of eight. S_1-Q_2-Q_3 or S_1-S_2-Q_3 patterns and an rS complex in Lead V_1 were frequently found in these residents of high altitudes.

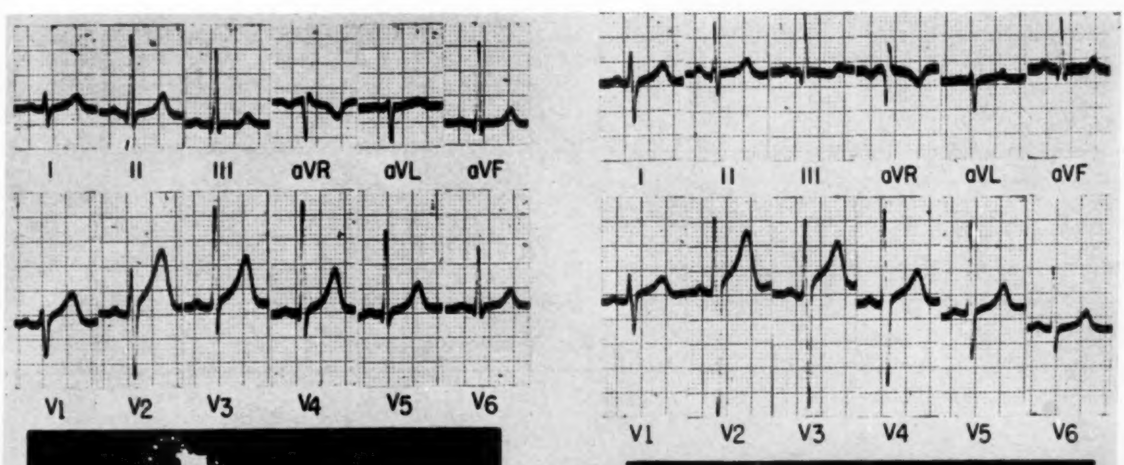

Fig. 2. *A*, A normal 23-year-old subject who lives at high altitudes. SÂQRS is in the right inferior posterior octant, and its frontal projection is oriented to +95°. The QRS loop is wide in the frontal view, and a clockwise rotation is seen in all three planes. The mid and final QRS vectors are approximately similar in magnitude. In this subject the following additional data were obtained: right ventricular systolic pressure, 43 mm. Hg; hemoglobin, 22 Gm. per cent; hematocrit, 60 per cent; arterial oxygen saturation, 82 per cent. *B*, A normal 22-year-old inhabitant of high altitudes. SÂQRS is in the right inferior posterior octant and its frontal projection is placed at +115°. The QRS loop is wide in the frontal plane and narrow (in profile) in the transverse view, which shows a figure-of-eight rotation.

Some subjects showed an rsr's' complex of low voltage and normal duration in Lead V_1. In some subjects (3.6 per cent) a peculiar projection of the mid and late QRS vectors made it impossible to determine the ÂQRS position, and diphasic QRS complexes were observed in all six extremity leads (Fig. 3,*A*).

2. SÂQRS in the left inferior posterior octant. This pattern was found in 25.2 per cent of the residents of high altitudes. In these individuals the spatial QRS loop was somewhat similar to that described in the previous group, but the frontal projection of the late QRS vectors was small (Fig. 4,*A*). In some subjects of this group, rsr's' complexes of low voltage and normal duration were found in Lead V_1 (Fig. 3,*B*). In a few cases (2.8 per cent), SÂQRS was in the left inferior anterior octant, and an Rs pattern was seen in Lead V_1 (Fig. 4,*B*).

Table I. *The ÂQRS position*

		15-20 years	*21-40 years*	*41-60 years*
Sea level	Mean ± S.E.	55 ± 2.2	45 ± 3.3	30 ± 3.3
	S.D.	22.3	32.4	32.7
	Extreme Values	−10 120	−30 120	−40 90
Morococha (14,900 ft.)	Mean ± S.E.	125 ± 6.8	105 ± 7.1	108 ± 7.9
	S.D.	46.1	70.2	78.5
	Extreme Values	60 −100	−35 −90	−80 −90
t		12.31*	7.77*	9.08*

t : t values calculated by Fisher's t-test.
*p < 0.001.

Table II. *The QRS scalar data in Lead* aV_R

		15-20 years	*21-40 years*	*41-60 years*
R' in aV_R (in mm. = 0.1 mv.) Sea level	Mean ± S.E.	1.1 ± 0.12	0.7 ± 0.09	0.3 ± 0.07
	S.D.	1.16	0.96	0.69
	Extreme Values	0 5	0 5	0 3.5
Morococha (14,900 ft.)	Mean ± S.E.	4.0 ± 0.32	2.8 ± 0.24	2.9 ± 0.18
	S.D.	2.24	2.35	1.82
	Extreme Values	1 10	0 11	0 8
t		10.59*	8.44*	12.95*
$\frac{R'}{Q \text{ or } S}$ in aV_R Sea level	Mean ± S.E.	0.2 ± 0.02	0.1 ± 0.02	0.1 ± 0.01
	S.D.	0.19	0.20	0.14
	Extreme Values	0 1	0 1.2	0 0.7
Morococha (14,900 ft.)	Mean ± S.E.	1.1 ± 0.16	0.8 ± 0.09	0.9 ± 0.11
	S.D.	1.13	0.99	1.09
	Extreme Values	0.1 7.0	0 5	0 2.5
t		8.30*	6.72*	7.71*

t : t values calculated by Fisher's t-test.
*p < 0.001.

Table III. *The QRS scalar data in precordial leads*

		15-20 years	*21-40 years*	*41-60 years*
R in V_1 (in mm. = 0.1 mv.)				
Sea level	Mean ± S.E.	3.8 ± 0.24	3.3 ± 0.19	2.2 ± 0.11
	S.D.	2.40	1.92	1.18
	Extreme Values	0 13	0 16	0 6
Morococha (14,900 ft.)	Mean ± S.E.	6.3 ± 0.56	3.5 ± 0.23	2.3 ± 0.15
	S.D.	4.01	2.38	1.52
	Extreme Values	1 23	0 12	0 7
t		4.90*	0.87	0.36
$\frac{R}{R+S}$ in V_1				
Sea level	Mean ± S.E.	0.3 ± 0.01	0.3 ± 0.01	0.3 ± 0.01
	S.D.	0.13	0.14	0.14
	Extreme Values	0 0.7	0 0.6	0 0.6
Morococha (14,900 ft.)	Mean ± S.E.	0.4 ± 0.03	0.3 ± 0.02	0.2 ± 0.02
	S.D.	0.19	0.20	0.17
	Extreme Values	0.1 0.8	0 1	0 0.8
t		5.17*	0.53	0.35
$\frac{R}{S}$ in V_5				
Sea level	Mean ± S.E.	5.5 ± 0.55	8.3 ± 0.79	12.8 ± 1.24
	S.D.	5.44	6.76	9.70
	Extreme Values	0.5 20	1 42	1.7 42
Morococha (14,900 ft.)	Mean ± S.E.	2.0 ± 0.23	3.4 ± 0.31	2.9 ± 0.29
	S.D.	1.61	3.05	2.94
	Extreme Values	0.5 9	0.1 16	0.4 11
t		4.42*	4.82*	9.38*
R in V_1 + S in V_5				
Sea level	Mean ± S.E.	8.1 ± 0.38	5.2 ± 0.28	3.1 ± 0.16
	S.D.	3.79	2.79	1.60
	Extreme Values	2 18	0.5 19	0.5 7
Morococha (14,900 ft.)	Mean ± S.E.	13.7 ± 0.77	8.8 ± 0.47	7.7 ± 0.39
	S.D.	5.45	4.70	3.98
	Extreme Values	11 28	1 26	2 30
t		7.30*	6.61*	10.8*

t : t values calculated by Fisher's t-test.
*p < 0.001.

3. SÂQRS in the right superior posterior octant: the S_1-S_2-S_3 pattern. In some adult dwellers of high altitudes (9.6 per cent), SÂQRS and the major portion of the spatial QRS loop were directed to the right, superiorly, and posteriorly (Fig. 5,*A*). In these subjects the late QRS vectors (QRS loop 3 or "basal" vectors) were predominant. The early QRS vectors were small and anteriorly oriented, whether to the left or to the right. The mid QRS vectors were also small. The frontal QRS loop was inscribed in a counterclockwise direction or in a figure of eight. The rotation of the horizontal QRS loop was in a clockwise fashion, with the mid QRS

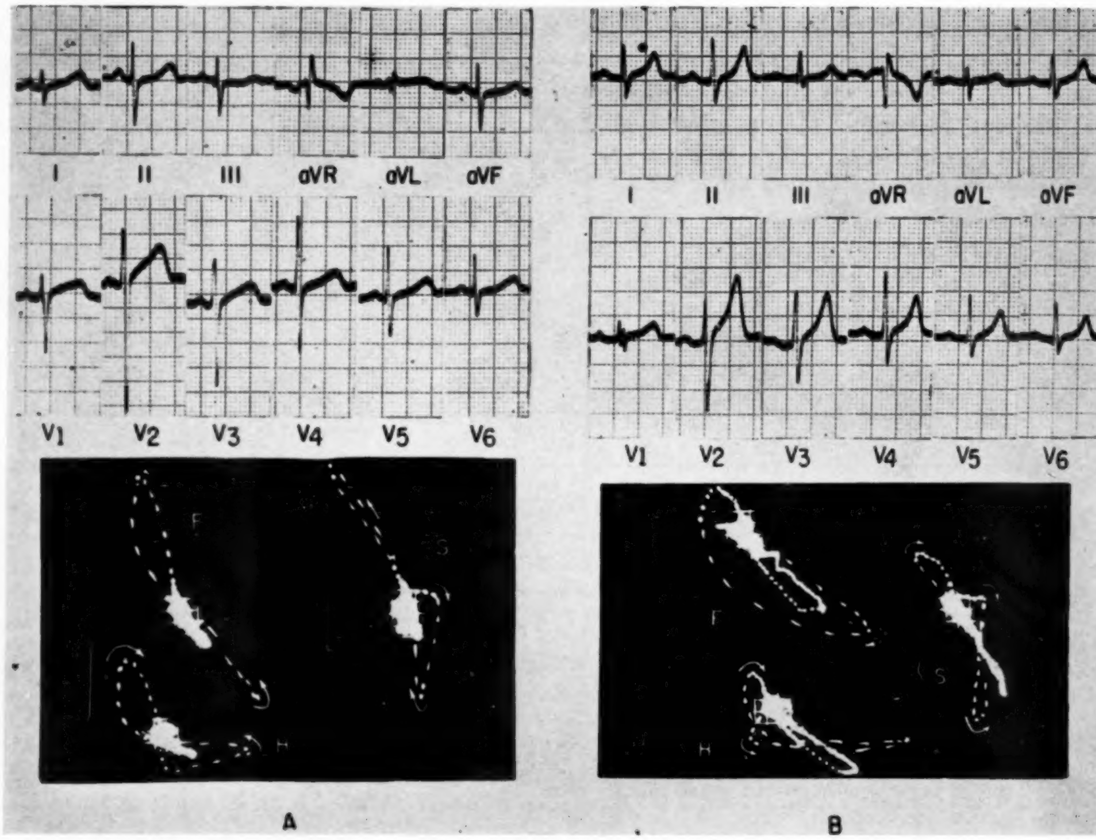

Fig. 3. *A*, A normal 25-year-old resident of high altitudes. ÂQRS is undetermined, and diphasic QRS complexes are present in all six limb leads. The QRS loop shows a figure-of-eight configuration in the transverse projection, and the final QRS vectors are of great magnitude. *B*, A healthy 35-year-old resident of high altitudes. ÂQRS points to the left. The final QRS vectors are large. The frontal QRS loop is wide and shows a clockwise rotation. An rsr′s′ pattern is present in Lead V_1, and the horizontal QRS loop rotates in a figure of eight.

vectors anteriorly oriented or in a figure of eight, and the mid QRS vectors posteriorly directed. An rS pattern was frequently found in all three standard limb leads (S_1-S_2-S_3 pattern or "concordant" S pattern) and in all six unipolar precordial leads.

4. SÂQRS in the left superior posterior octant. In these subjects (6.4 per cent), SÂQRS and the major portion of the spatial QRS loop were oriented to the left, superiorly, and posteriorly (Fig. 5,*B*). The QRS loop was similar to that of the previous group, but the mid QRS vectors were large and the final QRS vectors were only slightly oriented to the right. The inscription of the horizontal QRS loop was counterclockwise or in a figure of eight. The morphology of the QRS complex was also similar to that of the previous group, but diphasic or predominantly positive QRS complexes were frequently seen in Leads I and V_6.

5. SÂQRS in the right inferior anterior octant. In some residents of high altitudes (8.0 per cent), particularly those of the adolescent group, SÂQRS and the major portion of the spatial QRS loop were directed to the right, inferiorly, and anteriorly (Fig. 6,*A*). Vectors pointing in this direction ("right ventricular" vectors[16]) were predominant, whereas the left QRS vectors and the late QRS vectors were relatively small. The early QRS vectors were small and anteriorly directed, frequently to the left. The frontal and horizontal QRS loops were wide and inscribed in a clockwise direction. The configuration of the QRS complex in the extremity leads was similar to the one described in the first pattern. The QRS complex in Lead V_1 was predominantly

positive, and the most frequent configuration was Rs, with an early slurring in some cases. QRS complexes of rsR's', rR's, and qRs morphology were also seen in Lead V_1 and in the right additional chest leads. This diverse configuration was related to the variable orientation of the first portion of the QRS loop. A final S wave was a constant finding in Lead V_1 in residents of high altitudes. In some subjects (6.0 per cent) the increased "right ventricular" vectors were associated with large final QRS vectors (Fig. 6,*B*). In these cases, SÂQRS and the spatial QRS loop were in the right superior anterior octant, and S_1-S_2-S_3 or S_1-S_2-Q_3 patterns were associated with predominantly positive QRS complexes in Lead V_1.

Ventricular repolarization process. The adolescents and adults living at high altitudes showed a leftward, anterior, inferior orientation of the T loop and positive T waves in all precordial leads. Significant divergence between the QRS and T loops and a left posterior displacement of the J point ("secondary" ST-T changes) were not observed, despite the right anterior position of the QRS loop seen in some cases (Fig. 6,*A*). The upright T waves of the right precordial leads were abnormal in contour in approximately 20 per cent of the subjects in high altitudes. In some cases the T loop was in the left posterior inferior octant, and the T waves were negative, peaked, and symmetrical ("primary" T-wave changes) in the right

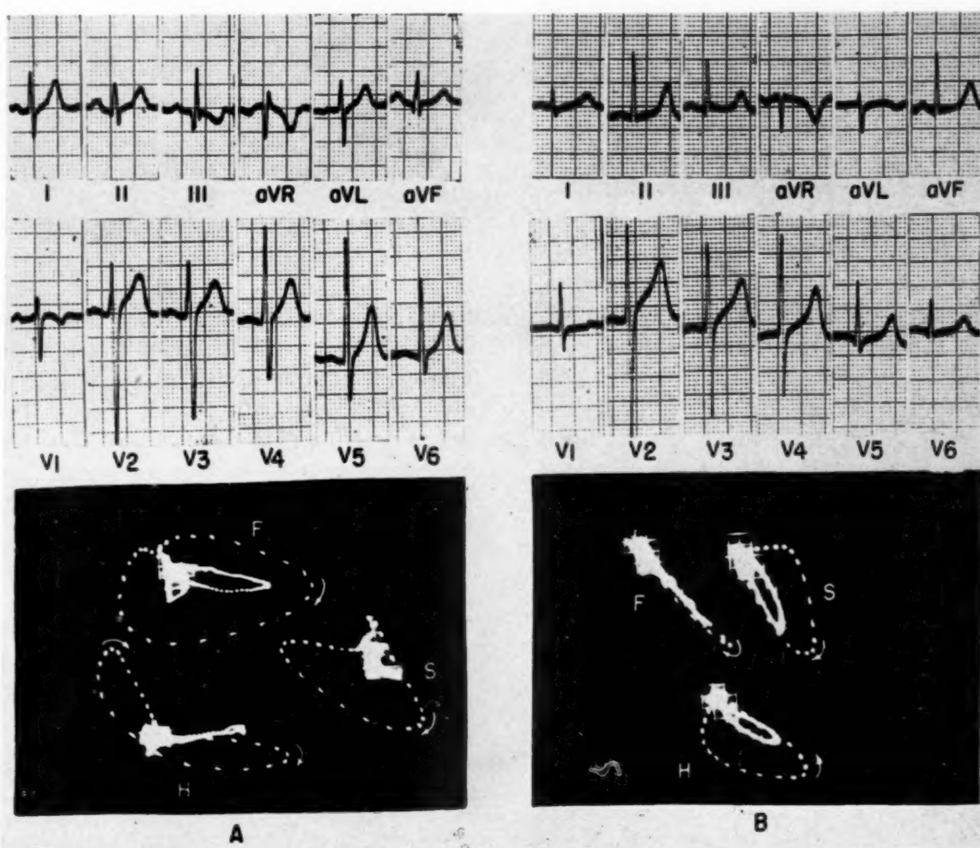

Fig. 4. *A*, A 28-year-old resident of high altitudes. SÂQRS is in the left inferior posterior octant, and its frontal projection points to +70°. The QRS morphology differs only slightly from that observed in normal adults at sea level. However, the frontal QRS is wide, and a clockwise rotation is seen in all three planes. The horizontal QRS loop shows two well-defined portions. *B*, A normal 31-year-old subject who lives at high altitudes. SÂQRS is in the left inferior anterior octant. The QRS configuration is normal in the limb leads, and an Rs complex is seen in Lead V_1. The horizontal QRS loop is anteriorly placed and shows a counterclockwise rotation. The final QRS vectors are small. In this subject the right ventricular systolic pressure was 37 mm. Hg, hemoglobin was 21 Gm. per cent, hematocrit was 62 per cent, and arterial oxygen saturation was 81 per cent.

precordial leads (Fig. 5,*A*). A comparison of downward T waves in the right precordial leads at sea level and those at high altitudes is shown in Table IV. Negative T waves in Lead V_1 were found less frequently with increasing age of the subjects at sea level. They were rare in Lead V_2 and were not observed in Lead V_3. At high altitudes a negative T wave was an infrequent finding in Lead V_1, but in those subjects who showed an "ischemic" T-wave pattern, negative T waves were also seen in Leads V_2 and V_3.

Discussion

Ventricular activation process. A considerable delay in the development of the QRS changes that normally occur during growth has been demonstrated in infants and children who live permanently at high altitudes.[6] In comparison with children, the adult dwellers at high altitudes show less right ÂQRS deviation, the mid QRS vectors are larger and show a less forward orientation, and the early QRS vectors are more frequently directed to the right. These vector changes indicate that as the age of the subject increases, the right ventricular preponderance diminishes. However, it occurs slowly and physiologic preponderance of the left ventricle is not attained at high altitudes.

Electrocardiographic and vectorcardiographic patterns are almost stereotyped in infancy and childhood at high altitudes, and SÂQRS is generally in the right anterior octants.[6] On the other hand, the ECG and VCG patterns are highly variable in adult inhabitants of the same altitudes. In most subjects the spatial orientation of the mid QRS vectors and the pathway of the horizontal QRS loop show similarities to those observed at sea level in transitional patterns of normal children between 3 months and 3 years of age.[6] However, at high altitudes the final QRS vectors are of great magnitude, which accounts for the rS complex in Lead V_1 and the SÂQRS position in the right inferior posterior octant. Patterns of this group are similar to Grishman's Type I described in some congenital heart diseases with a mild right ventricular hypertension,[17-19] and they also resemble Deglaude's Types I and II reported in mitral stenosis with a mild pulmonary hypertension.[20] However, the late QRS vectors are usually of greater magnitude in healthy residents of high altitudes, and for this reason an rS pattern in Lead V_1 is more frequently found in these subjects than in persons with mitral stenosis or congenital cardiac malformations. At high altitudes these patterns are associated with a mild right ventricular hypertension, and they should be considered as one type of systolic overloading of the right ventricle in spite of the rS or rsr's' complexes in Lead V_1.

In residents of high altitudes who show SÂQRS in the left inferior posterior octant the electrocardiogram resembles that seen in normal adults at sea level, but the vectorcardiogram differs only slightly from that described in the previous pattern. This singular finding in the presence of right ventricular hypertrophy has been rarely reported.[19] The pattern of SÂQRS in the left inferior anterior octant and an Rs complex in Lead V_1 resembles that frequently observed at sea level in normal children up to 3 years of age.[6] SÂQRS

Table IV. *Distribution, in per cent, of the negative T waves in the right precordial leads*

	Sea level			*Morococha (14,900 ft.)*		
	15-20 years (%)	*21-40 years* (%)	*41-60 years* (%)	*15-20 years* (%)	*21-40 years* (%)	*41-60 years* (%)
Lead V_1	58	23	13	22	8	8
Lead V_2	1	1	0	8	5	3
Lead V_3	0	0	0	6	0	2

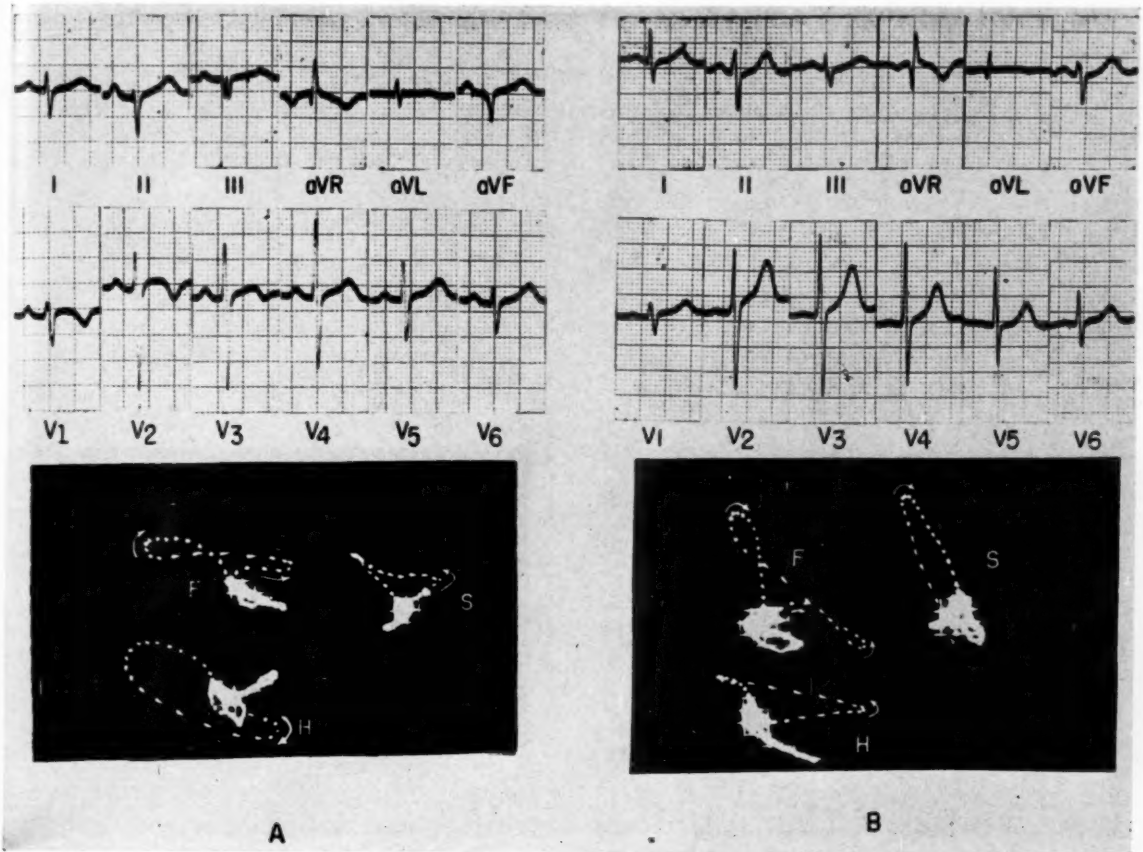

Fig. 5. *A*, A normal 27-year-old dweller at high altitudes. SÂQRS is in the right superior posterior octant, and its frontal projection points to $-120°$. An S_1-S_2-S_3 pattern is present. An rS complex is seen in all six precordial leads. The final QRS vectors are predominant. The frontal QRS loop exhibits a figure-of-eight rotation, and the horizontal QRS loop rotates clockwise, with the mid QRS vectors oriented anteriorly. An "ischemic" T wave pattern is seen in the right precordial leads. In this subject the right ventricular systolic pressure was 42 mm. Hg, hemoglobin was 21 Gm. per cent, hematocrit was 61 per cent, and arterial oxygen saturation was 82 per cent. *B*, A normal 38-year-old inhabitant of high altitudes. SÂQRS is in the left superior posterior octant, and its frontal projection is oriented to $-75°$. The QRS configuration is similar to that seen in *A*, but an Rs complex is present in Lead I and in the left precordial leads. The final QRS vectors are predominant, but they are only slightly oriented to the right. The QRS-loop rotation is counterclockwise in the transverse projection, and figure of eight in the frontal view.

orientation in the left superior posterior octant is observed in older adults and in subjects who lived the greater part of their lives in altitudes lower than that of Morococha. Similar patterns in the presence of right ventricular hypertrophy have been rarely reported in chronic cor pulmonale,[21] and in some congenital heart diseases.[17,18]

Electrocardiographic and vectorcardiographic patterns associated with SÂQRS in the right superior posterior octant have also been described in chronic pulmonary heart disease and in some congenital cardiac malformations.[22-31] They are similar in some respects to Grishman's Type III* reported in some congenital heart diseases with severe right ventricular hypertension.[17,18] However, in most of Grishman's cases, SÂQRS was oriented anteriorly, and positive QRS complexes were present in Lead V_1. In our residents of high altitudes an rS complex in Lead V_1 and a mild right ventricular hypertension were common findings. The electrogenesis of the S_1-S_2-S_3 syndrome has been extensively discussed, and frequently it was ascribed to a marked clockwise rotation of the heart around its longitudinal axis, with posterior displacement of the apex.[32-34]

*In a recent paper from Grishman's laboratory[19] this pattern has been included in the Type II.

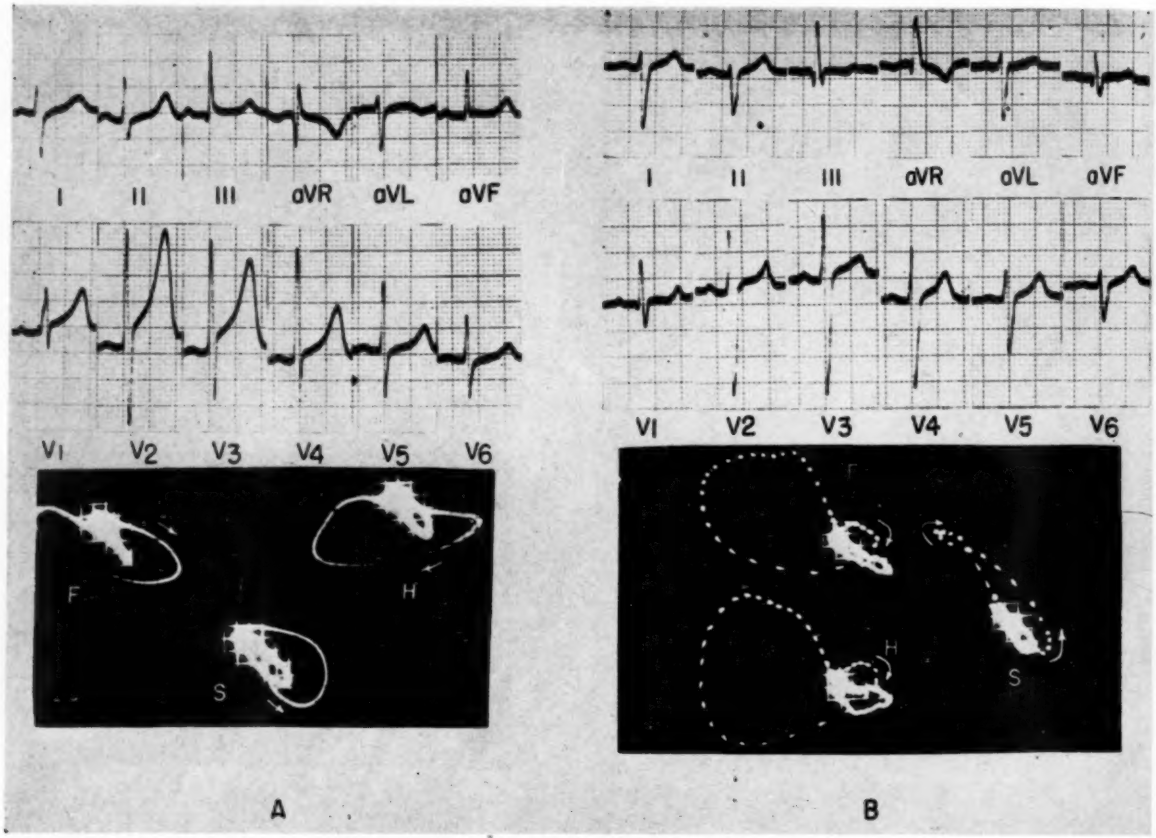

Fig. *6*. *A*, A 22-year-old healthy resident of high altitudes. SÂQRS is in the right inferior anterior octant. The right precordial leads show positive QRS complexes and positive T waves. The frontal and horizontal QRS loops are wide and rotate in a clockwise direction. In this subject the right ventricular systolic pressure was 50 mm. Hg, hemoglobin was 23 Gm. per cent, hematocrit was 66 per cent, and arterial oxygen saturation was 79 per cent. ***B*,** A healthy 20-year-old resident of high altitudes. SÂQRS is in the right superior anterior octant. The right QRS vectors and the final QRS vectors are large. An S_1-S_2-S_3 pattern is present, and Lead V_1 shows a QRS complex with a late R wave (qRs configuration).

The vectorial observations[35] and the epicardial leads in man[36,37] have shown in these cases an unusual sequence of ventricular activation in which the late QRS vectors are predominant. In our subjects the large projection of the late QRS vectors in all three planes does indicate a true spatial increase of these vectors. For this reason, we cannot consider that a special position of the heart is an important determining factor of such a pattern. Furthermore, the roentgen examination and the anatomic study do not disclose any peculiarities in the heart position in subjects with this pattern. Special changes in the tissues surrounding the heart, which might explain these bizarre cases by modifications of the conducting media, were not apparent in these subjects. The S_1-S_2-S_3 pattern seen in some healthy people who live permanently at high altitudes should be considered as another type of systolic overloading of the right ventricle, in spite of the rS complex in Lead V_1.

The pattern associated with SÂQRS in the right inferior anterior octant resembles one type described by Cabrera in systolic overloading of the right ventricle,[38,39] some examples of Grishman's Type II,[17-19] and Deglaude's Types III and IV.[20] However, in cases reported by these and other authors the QRS pattern was frequently associated with "secondary" ST-T changes and was seen in the presence of accentuated right ventricular hypertrophy,[17-19,40-45] with the ventricular systolic pressure similar to, or higher than, that of the systemic circulation.[17-20,43] However, in healthy people who live permanently at high altitudes this QRS pattern is not associated with

"secondary" ST-T changes and is found in the presence of only a mild right ventricular hypertension. This pattern is similar to that seen in infants and children of the same altitudes,[6] and its persistence until adult age suggests that a mild right ventricular hypertension, if maintained throughout infancy and childhood, can arrest to an important degree the normal pattern of development of the QRS changes expected with aging. The same explanation is probably valid for the presence of "marked" signs of right ventricular preponderance in some congenital heart diseases with a mild right ventricular hypertension.[46-48] This, however, does not occur when the right ventricular hypertrophy is acquired after the normal left ventricular preponderance has been attained, for example, in chronic cor pulmonale and mitral stenosis. In these cases a high degree of right ventricular pressure is required in order to produce accentuated signs of right ventricular hypertrophy.[49-51]

The five mentioned QRS patterns do not represent different types of ventricular activation. They are rather varieties of a peculiar ventricular activation process which exhibits two principal characteristics, an increased magnitude of the terminal QRS vectors and a delay in the development of the QRS changes expected with aging. The association in variable proportion of these two features could explain the variable electrocardiograms and two-dimensional vectorcardiograms observed in adolescence and adulthood at high altitudes. Rotta and Lopez[4] described four electrocardiographic patterns in normal adult inhabitants of high altitudes. The pattern reported as "right ventricular hypertrophy" is similar to the one described by us in which SÂQRS is in the right anterior octants. The pattern "suggestive of right ventricular hypertrophy" corresponds to S_1-S_2-S_3 syndrome, and it is ascribed by the above-mentioned authors to positional changes of the heart. Their "normal" pattern is similar to that described by us in which SÂQRS is in the left inferior posterior octant, but we did not find normal vectorcardiograms in the residents of high altitudes of this group. The pattern with SÂQRS in the right inferior posterior octant, the most common in adults of high altitudes, is not commented upon by these authors. A pattern with SÂQRS in the left superior posterior octant was not studied. "Right bundle branch block, incomplete or complete" is the fourth pattern pointed out by these authors, and it will be discussed later. This classification implies different types of ventricular activation, and it ascribes an important role to the cardiac position in the genesis of the electrocardiograms at high altitudes. The results of our investigation are not in agreement with this hypothesis.

Complete right bundle branch block was a rare finding in normal dwellers of high altitudes. An R-R′ complex of normal duration and low voltage, frequently of rsr′s′ configuration, was found in Lead V_1 in 8.5 per cent of the subjects studied at high altitudes. This pattern probably represents a transitional stage in the pattern of development of QRS changes throughout life. Various features support this hypothesis. (1) An r′-V_1 transitional pattern can be seen in normal children who live at sea level, whereas at high altitudes the same pattern is not found until adult age. On the other hand, native residents of high altitudes with an Rs pattern in Lead V_1 show the r′-V_1 pattern after one or more years of residence at sea level.[52] This phenomenon resembles that reported after operation in certain heart diseases with right ventricular hypertrophy.[53-57] (2) The final portion of the QRS loop does not show the characteristics commonly seen in clinical and experimental right bundle branch block.[58-61] (3) The intracavity leads of the right ventricle recorded as recommended by Sodi-Pallares and associates,[62,63] are frequently normal in subjects with an r′-V_1 pattern at high altitudes.[52] As for the R′-V_1 pattern with a predominantly positive QRS complex (rsR′s′, rR′s, or qRs configurations) seen in some subjects who ive at high altitudes, this is probably related to the association of right ventricular hypertrophy and a certain degree of right bundle branch block.[61]

Ventricular repolarization process. The greater frequency of positive T waves in the right precordial leads at high altitudes is probably related to chronic right ventricular overloading, as is seen in infancy

and childhood.[6,64,65] The "ischemic" T-wave pattern seen in the right precordial leads of some residents of high altitudes is also frequently observed in newcomers to these places,[66,67] and in natives who lose their adaptation to high altitudes.[52] In these subjects the "ischemic" T-wave pattern is related to subacute right ventricular overloading. When this pattern appears in normal residents of high altitudes, it probably constitutes an early index of disadaptation to high altitudes.

The right ventricular hypertrophy of high altitudes and its relation to the mechanisms of acclimatization. Electrocardiographic and vectorcardiographic characteristics of the people who live permanently at high altitudes are associated with a moderate increase in the weight of the right ventricle; the thickest portion of the right ventricular wall is the outflow tract,[68] which agrees with the increased magnitude of the late QRS vectors. A mild pulmonary hypertension and a normal cardiac output have been found in the same subjects.[11] After birth, the hypoxia of high altitudes maintains the fetal structure of the small pulmonary arteries and arterioles,[69] and as a consequence an elevated pulmonary vascular resistance and a mild pulmonary hypertension are also maintained. Polycythemia, an early adaptive hematological mechanism,[9] and an increased pulmonary blood volume[10] probably also contribute to the increase of pulmonary vascular resistance and pulmonary pressure. The pulmonary hypertension maintained throughout life explains the peculiar characteristics of the electrical activity of the heart at high altitudes: a delay in the pattern of development of the QRS changes with aging, an increased magnitude of the terminal QRS vectors, and a high incidence of positive T waves in the right precordial leads.

The electrocardiograms and vectorcardiograms of the adolescent and the adult who live permanently at high altitudes are not similar to those of the normal adolescent and adult at sea level. The electrocardiographic measurements show statistically significant differences between the two places. Therefore, a high-altitude environment is an important cause of electrocardiographic and vectorcardiographic variability in healthy people. It is important to remember this in evaluating the electrocardiographic and vectorcardiographic findings in heart diseases at high altitudes.[52]

Summary

1. Electrocardiographic and vectorcardiographic observations were obtained in 550 normal subjects, 300 at sea level and 250 in Morococha, 14,900 feet above sea level. A comparative study was made in three age groups: the age range was 15 to 60 years.

2. The ventricular activation process shows significant differences between the two places studied. In adolescent and adult inhabitants of high altitudes there is a wide range in SÂQRS direction, the configuration of the QRS complex is highly variable both in the limb and precordial leads, and the two-dimensional projections of the spatial QRS loop show wide diversity.

3. Five principal QRS patterns are described according to the spatial SÂQRS orientation. These patterns do not represent different types of ventricular activation. They are varieties of a peculiar activation process which exhibits two principal characteristics: a delay in the pattern of development of the QRS changes that normally occur with aging, and an increasing magnitude of the terminal QRS vectors.

4. The most common pattern in adults of high altitudes shows SÂQRS in the right inferior posterior octant, an rS complex in Lead V_1, and S_1-Q_2-Q_3 or S_1-S_2-Q_3 patterns in extremity leads. The S_1-S_2-S_3 pattern is also observed, and it is related to predominant late QRS vectors and not to a special cardiac position. Predominantly positive QRS complexes in Lead V_1 are infrequent in adults of high altitudes. The r'-V_1 pattern seen in some subjects who live at high altitudes probably represents a transitional stage in the pattern of development of QRS throughout life.

5. In adults at high altitudes, right ventricular preponderance is less than in children at the same altitudes, but the physiologic preponderance of the left ventricle seen at sea level does not occur even in the older adults. The moderate right ventricular hypertrophy of high altitudes

is probably related to anatomic and functional changes that take place in the pulmonary circulation as a consequence of the process of acclimatization.

6. The electrocardiographic and vectorcardiographic characteristics of the adolescents and adults who live permanently at high altitudes are not similar to those of normal adolescents and adults who live at sea level. Therefore, a high-altitude environment is an important cause of electrocardiographic and vectorcardiographic variability in healthy people.

The authors are indebted to Dr. Víctor Hernandez and to Mr. Julio Cruz for their valuable help with statistical analysis of the data.

REFERENCES

1. Capdehourat, E. L.: Estudios sobre la biología del hombre de la altitud, Buenos Aires, 1937, Ministerio de Justicia e Instrucción Pública.
2. Rotta, A.: Physiologic conditions of the heart in the natives of high altitude, Am. Heart J. **33**:669, 1947.
3. Cosío, G., and Corigliano, J.: Compromiso ventricular derecho en mineros de altura, Rev. peruana cardiol. **5**:25, 1956.
4. Rotta, A., and Lopez, A.: Electrocardiographic patterns in man at high altitudes, Circulation **5**:719, 1959.
5. Taquini, A. C.: El corazón pulmonar, Buenos Aires, 1954, Editorial El Ateneo.
6. Peñaloza, D., Gamboa, R., Dyer, J., Echevarría, M., and Marticorena, E.: The influence of high altitudes on the electrical activity of the heart. I. Electrocardiographic and vectorcardiographic observations in the newborn, infants, and children, Am. Heart J. **59**:111, 1960.
7. Hurtado, A., and Aste-Salazar, H.: Arterial blood gases and acid-base balance at sea level and at high altitudes, J. Appl. Physiol. **1**:304, 1948.
8. Hurtado, A., Merino, C., and Delgado, E.: Influence of anoxemia on the hemopoietic activity, Arch. Int. Med. **75**:284, 1945.
9. Reynafarje, C., Lozano, R., and Valdivieso, J.: The polycythemia of high altitudes: iron metabolism and related aspects, Blood **14**:433, 1959.
10. Monge, C., Cazorla, A., Whittembury, G., Sakata, Y., and Rizo-Patron, C.: A description of the circulatory dynamics in the heart and lungs of people at sea level and at high altitude by means of the dye dilution technique, Acta physiol. latinoam. **6**:15, 1956.
11. Rotta, A., Canepa, A., Hurtado, A., Velasquez, T., and Chavez, R.: Pulmonary circulation at sea level and at high altitudes, J. Appl. Physiol. **9**:328, 1956.
12. Hurtado, A., Velasquez, T., Reynafarje, C., Lozano, R., Chavez, R., Aste-Salazar, H., Reynafarje, B., Sanchez, C., and Muñoz, J.: Mechanisms of natural acclimatization. Studies on the native resident of Morococha, Perú, at an altitude of 14,900 feet, Report to the U.S.A.F. School of Aviation Medicine, 1956.
13. Reynafarje, B.: Estudios de química tisular en la hipoxia, Simposios y Conferencias, XXI Congreso Internacional de Ciencias Fisiológicas, Buenos Aires, 1959.
14. Grishman, A., Borun, E. R., and Jaffe, H. L.: Spatial vectorcardiography. I. Technique for the simultaneous recording of the frontal, sagittal and horizontal projections, Am. Heart J. **41**:438, 1951.
15. Duchosal, P. W., and Sulzer, R.: La vectocardiographie, Basel, 1949, S. Karger.
16. Peñaloza, D., and Transchesi, J.: The three main vectors of the ventricular activation process in the normal human heart. I. Its significance, Am. Heart J. **49**:51, 1955.
17. Grishman, A., and Scherlis, L.: Spatial vectorcardiography, Philadelphia, 1952, W. B. Saunders Company.
18. Lasser, R. P., Borun, E. R., and Grishman, A.: Spatial vectorcardiography: right ventricular hypertrophy as seen in congenital heart disease, Am. Heart J. **42**:370, 1951.
19. Donoso, E., Sapin, S. O., Braunwald, E., and Grishman, A.: A study of the electrocardiogram and vectorcardiogram in congenital heart disease. II. Vectorcardiographic criteria for ventricular hypertrophy, Am. Heart J. **50**:674, 1955.
20. Deglaude, L., and Laurens, P.: Étude vectographique de la surcharge ventriculaire droite dans le retrécissement mitral, Arch. mal. coeur **48**:129, 1955.
21. Zuckermann, R., Cabrera, E., Fishleder, B. L., and Sodi-Pallares, D.: Electrocardiogram in chronic cor pulmonale, Am. Heart J. **35**:421, 1948.
22. Burstein, J., and Ellenbogen, L.: Electrocardiograms in which the main initial ventricular deflections are directed downward in the standard leads, Am. Heart J. **16**:165, 1938.
23. Wilburne, M., and Langendorf, R.: Significance of the electrocardiogram with prominent S wave in leads I, II, and III, J. Lab. & Clin. Med. **28**:303, 1942.
24. Schwartz, S. P., and Marcus, J.: The electrocardiogram in pulmonary tuberculosis, Am. Rev. Tuberc. **46**:35, 1942.
25. Goldberger, E., and Schwartz, S. P.: Electrocardiograms in which the main ventricular deflections are directed downward in the standard leads, Am. Heart J. **29**:62, 1945.
26. Goldberger, E., and Schwartz, S. P.: Electrocardiograms in chronic pulmonary disease, Am. Rev. Tuberc. **53**:34, 1946.
27. Fershing, J., and Baker, L.: Clinical analysis of the S wave pattern electrocardiogram, Am. Heart J. **35**:106, 1948.
28. Carouso, G., Tiltmant, J., and Lenègre, J.: Signification des ondes S_1, S_2, et S_3 predominantes, Arch. mal. coeur **42**:418, 1949.
29. Donzelot, E., Metianu, C., Durand, M., and Vlad, P.: L'axe electrique moyen de QRS dans le dernier sextant (−150° à −90°) chez les congenitaux (étude de 30 cas), Arch. mal. coeur **43**:203, 1950.

30. Levinthal, J., and Purdy, A.: Electrocardiograms with deep S waves in all three standard leads, Am. J. Dis. Child. **81**:59, 1951.
31. Lasser, R. P., and Grishman, A.: Vectorcardiograms obtained in patients with right ventricular hypertrophy whose electrocardiograms display an unusual axis deviation or left axis deviation. IV, Am. Heart J. **41**:901, 1951.
32. Gardberg, M., and Ashman, R.: The QRS complex of the electrocardiogram, Arch. Int. Med. **72**:210, 1943.
33. Wilson, F. N., Johnston, F. D., Rosenbaum, F. F., Erlanger, H., Kossmann, C. E., Hecht, H. H., Cotrim, N., Menezes de Oliveira, R., Scarsi, R., and Barker, P. S.: The precordial electrocardiogram, Am. Heart J. **27**:19, 1944.
34. Goldberger, E.: Unipolar lead electrocardiography and vectorcardiography, Philadelphia, 1953, Lea & Febiger.
35. Grant, R. P.: Clinical electrocardiography. The spatial vector approach, New York, 1957, McGraw-Hill Book Company, Inc.
36. Barbato, E., Pileggi, F., Debes, A. C., Fujioka, T., Magalhaes, M. S., Tranchesi, J., San Juan, E., and Décourt, L.: Study of the sequence of ventricular activation and the QRS complex of the normal human heart using direct epicardical leads, Am. Heart J. **55**:867, 1958.
37. Barbato, E., Debes, A. C., Pileggi, F., Fujioka, T., Paula e Silva, P., and Décourt, L.: Diaphragmatic juxtacardiac leads: their value in the study of the spread of activation and the QRS complex of the heart's diaphragmatic surface, Am. Heart J. **57**:263, 1959.
38. Cabrera, E., and Monroy, J. R.: Systolic and diastolic loading of the heart. Part II. Electrocardiographic data, Am. Heart J. **43**:669, 1952.
39. Cabrera, E., and Gaxiola, A.: A critical reevaluation of systolic and diastolic overloading patterns, Prog. Cardiovas. Dis. **2**:219, 1959.
40. Lamb, L. E., Grosgurin, J. R., and Duchosal, P. W.: Vectorcardiographic studies of ventricular hypertrophy, Cardiologia **28**:65, 1956.
41. Cabrera, E., Gaxiola, A., and Eisenberg, P.: El vectocardiograma en los crecimientos ventriculares derechos tipo sobrecarga sistólica, Arch. Inst. cardiol. Mexico **28**:469, 1958.
42. Duchosal, P. W., and Grosgurin, J. R.: Atlas d'électrocardiographie et de vectocardiographie, Basle and New York, 1959, S. Karger.
43. Peñaloza, D., Tranchesi, J., Marsico, F., Limon-Lason, R., and Sodi-Pallares, D.: Vectorial analysis of the electrocardiogram in right ventricular hypertrophy. I. Congenital heart disease with pure or associated pulmonary stenosis, Second Congress of S.I.B.I.C., Acapulco, Mexico, April, 1954.
44. Sodi-Pallares, D., and Marsico, F.: The importance of electrocardiographic patterns in congenital heart disease, Am. Heart J. **49**:202, 1955.
45. Portillo, B., and Sodi-Pallares, D.: Semiología electrocardiográfica de la hipertrofia ventricular y sobrecarga sistólica del ventrículo derecho en los padecimientos congénitos del corazón, Principia Cardiológica **6**:231, 1959.
46. Gordon, A., and Goldberg, H.: Correlation of the electrocardiographic pattern of right heart strain and evidence of right ventricular hypertension in congenital heart disease, Am. Heart J. **42**:226, 1951.
47. Houssay, H. E. J., and Dexter, L.: Physiological factors involved in the production of right ventricular hypertrophy, Paper presented at the IV Interamerican Congress of Cardiology, Buenos Aires, 1952.
48. Cosby, R. S., Levinson, D. C., Dimitroff, S. P., Oblath, R. W., Herman, L. M., and Griffith, G. C.: The electrocardiogram in congenital heart disease and mitral stenosis, Am. Heart J. **46**:670, 1953.
49. Johnson, J. B., Ferrer, M. I., and Cournand, A.: The relation between electrocardiographic evidence of right ventricular hypertrophy and pulmonary arterial pressure in patients with chronic pulmonary disease, Circulation **1**:536, 1950.
50. Scott, R. C., Kaplan, S., Fowler, N. O., Helm, R. A., Wescot, R. N., Walker, I. C., and Stiles, W. T.: The electrocardiographic pattern of right ventricular hypertrophy in chronic cor pulmonale, Circulation **11**:927, 1955.
51. Torner-Soler, M., Balaguer-Vintró, I., and Gibert-Queraltó, G.: Elevated right ventricular pressure. Its relation to the pattern of right ventricular hypertrophy, Am. Heart J. **49**:538, 1955.
52. Peñaloza, D., et al.: Unpublished observations.
53. Blount, S. G., McCord, M. C., Mueller, H., and Swan, H.: Isolated valvular pulmonic stenosis. Clinical and physiologic response to open valvuloplasty, Circulation **10**:161, 1954.
54. Landtman, B.: Postoperative changes in the electrocardiogram in congenital heart disease. I. Pure pulmonic stenosis, Circulation **10**:859, 1954.
55. Walker, W. J., Mattingly, T. W., Pollock, B. E., Carmichael, D. B., Inmon, T. W., and Forrester, R. H.: Electrocardiographic and hemodynamic correlation in atrial septal defect, Circulation **12**:786, 1955.
56. Kahn, M., Bleifer, S. B., Grishman, A., and Donoso, E.: The vectorcardiogram and electrocardiogram before and after valvulotomy for pulmonic stenosis, Am. Heart J. **58**:327, 1959.
57. Beregovich, J., Bleifer, S., Donoso, E., and Grishman, A.: Vectorcardiographic and electrocardiographic changes following surgical correction of atrial septal defect, Am. Heart J. **59**:329, 1960.
58. Lasser, R. P., and Grishman, A.: Spatial vectorcardiography: right bundle branch block. VIII, Am. Heart J. **42**:513, 1951.
59. Cabrera, E., Garcia-Font, R., Gaxiola, A., and Pileggi, F.: The vectorcardiogram of ventricular activation in chronic coronary heart disease, Am. Heart J. **55**:557, 1958.
60. Peñaloza, D., Gamboa, R., and Sime, F.: Experimental right bundle branch block in the human heart. Electrocardiographic and vectorcardiographic observations in the heart without hypertrophy. Presented to the International Symposium on Atherosclerosis and

Coronary Heart Disease, México, D. F., September, 1959.

61. Peñaloza, D., Gamboa, R., and Sime, F.: Experimental right bundle branch block in the human heart. Electrocardiographic and vectorcardiographic observations in the heart with right ventricular hypertrophy. Presented to the Symposium on Electrocardiography, Sixth Interamerican Congress of Cardiology, Río de Janeiro, August, 1960.
62. Miquel, C., Sodi-Pallares, D., Cisneros, F., Pileggi, F., Medrano, G. A., and Bisteni, A.: Right bundle branch block and right ventricular hypertrophy, Am. J. Cardiol. **1**:57, 1958.
63. Del Rio, R., Medrano, G., Rubio, V., Perez Olea, J., Soni, J., and Sodi-Pallares, D.: Right bundle branch block with right ventricular hypertrophy, Am. J. Cardiol. **4**:294, 1959.
64. Ziegler, R. F.: The importance of positive T waves in the right precordial electrocardiogram during the first year of life, Am. Heart J. **52**:533, 1956.
65. Marsico, F., Cardenas, M., Pileggi, F., and Sodi-Pallares, D.: La onda T positiva en VI como signo de hipertrofia ventricular derecha del niño, Arch. Inst. cardiol. México **27**:323, 1957.
66. Peñaloza, D., and Echevarría, M.: Electrocardiographic observations on ten subjects at sea level and during one year of residence at high altitudes, Am. Heart J. **56**:811, 1957.
67. Peñaloza, D., Echevarría, M., Marticorena, E., and Gamboa, R.: Early electrocardiographic changes produced by ascending to high altitudes, Am. Heart J. **56**:493, 1958.
68. Campos, J., and Iglesias, B.: Observaciones anátomo-patológicas en 49 personas normales nativas y residentes en la altura (3,700-5,000 mts.) muertas en accidente, Rev. latinoam. anat. patol. **1**:109, 1957.
69. Arias, J., Saldaña, M., Peñaloza, D., and Gamboa, R.: Unpublished observations.

Case reports

Endocardial fibroelastosis in one of monozygotic twins

Harold E. Stadler, M.D.
Indianapolis, Ind.

Disparity in the cardiac status of monozygotic twins has been reported in the past, with a different lesion being present in the two instances.[1,2] The present report concerns a third lesion observed in one of "identical" twins. Fortunately, the babies under discussion were closely observed shortly after birth, and the details of their physical appearance carefully noted. The placental structure was also described in detail. The importance of this data became evident when the ravages of a disease process resulted in a loss of the close resemblance.

Dr. James Hawk, who delivered the infants, wrote as follows: "It was known that this patient was larger than average for the estimated gestation; however, I had not been able to hear two fetal hearts even though I suspected a multiple pregnancy. The patient refused to have an x-ray made. Labor occurred two weeks early and both babies reacted well, the first one being somewhat smaller than the second. The mother was Rh-negative, so cord blood from each infant was sent to the laboratory. Examination of the placentas revealed that they were fused and that there was only one chorion but two amnions and that portions of the membranes separating the babies were very thin and seemed to be in only two layers."

Baby A weighed 4 pounds and 2 ounces, and Baby B weighed exactly 1 pound more (5 pounds and 2 ounces). Examination of the two infants was entirely negative, and they appeared to be identical. The blood groups were found to be the same: blood group A, Rh subtypes C, D, and E negative. The anti-M, anti-N, c, and e were positive. The Coombs test was negative in both instances, and routine blood counts were within normal limits. The smaller infant gained well and was dismissed at the age of 3 weeks, at which time his weight was 5 pounds and 9 ounces. He was said to have weighed 8 pounds at the age of 6 weeks.

The infants were not observed again until Nov. 19, 1959, at which time (age 16 months) there was a striking difference in the appearance of the twins. Twin A weighed 19¼ pounds and was 30 inches long. Air hunger was evident, with a grunt on expiration, retraction of the intercostal spaces and episternal notch on inspiration, and an ashen-gray color of the skin. There was no clubbing of the fingers or toes. The heart was enlarged in all diameters, and there was a thrill particularly marked at the apex. The rhythm was regular, but the rate was quite consistently 160 per minute. A generalized harsh systolic murmur was most prominent at the mitral area. The rapid rate precluded definition of gallop rhythm. The breath sounds were subdued over the bases of the lungs, and showers of fine moist râles could be heard. Hepatosplenomegaly was not present, and there was no peripheral edema.

Twin A was said to have never thrived as well as his sibling. Pallor had been present since the age of 4 months. Four days prior to this examination, he had become anorexic and had developed an expiratory grunt which was quite progressive in nature. Cough had been moderate, but restlessness and irritability had been severe.

Twin B at this time weighed 22½ pounds and was 31½ inches in length. He showed no defect except for intense pallor of the skin and mucous membranes. His hemoglobin was found to be 7.8 Gm. per hundred cubic centimeters of blood.

Twin A was hospitalized on Nov. 13, 1959. The hemoglobin was 7 Gm. (hematocrit, 29); the leukocyte count was 8,900 with normal differential.

From the Department of Pediatrics, The Community Hospital, Indianapolis, Ind.
Received for publication May 26, 1960.

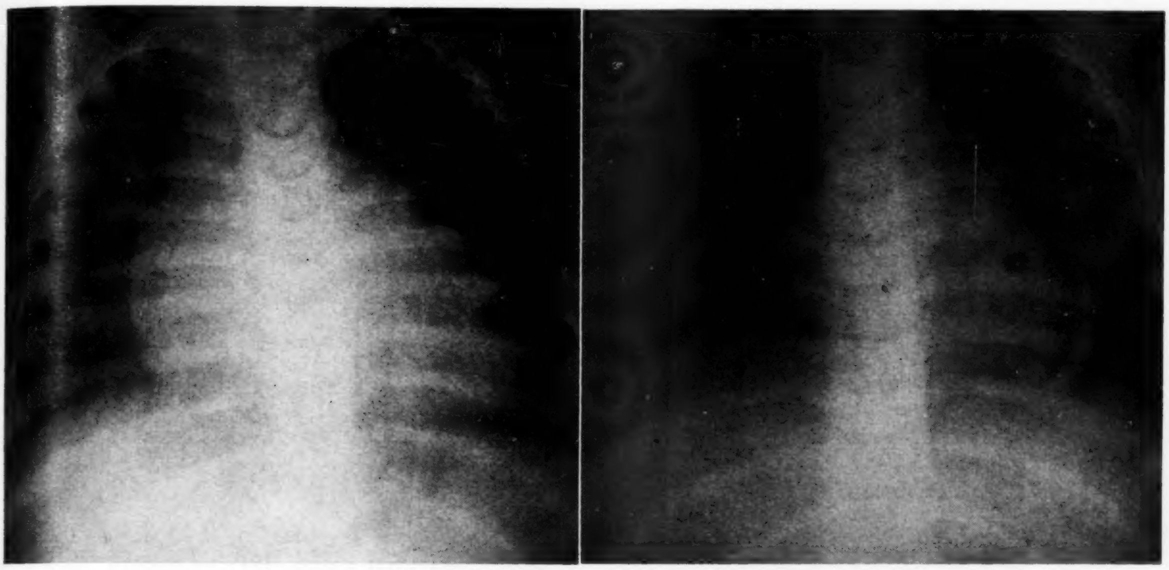

Fig. *1.* Radiograms of the chests of the twins, showing marked enlargement of the heart of the affected child. *Left:* Twin A. *Right:* Twin B.

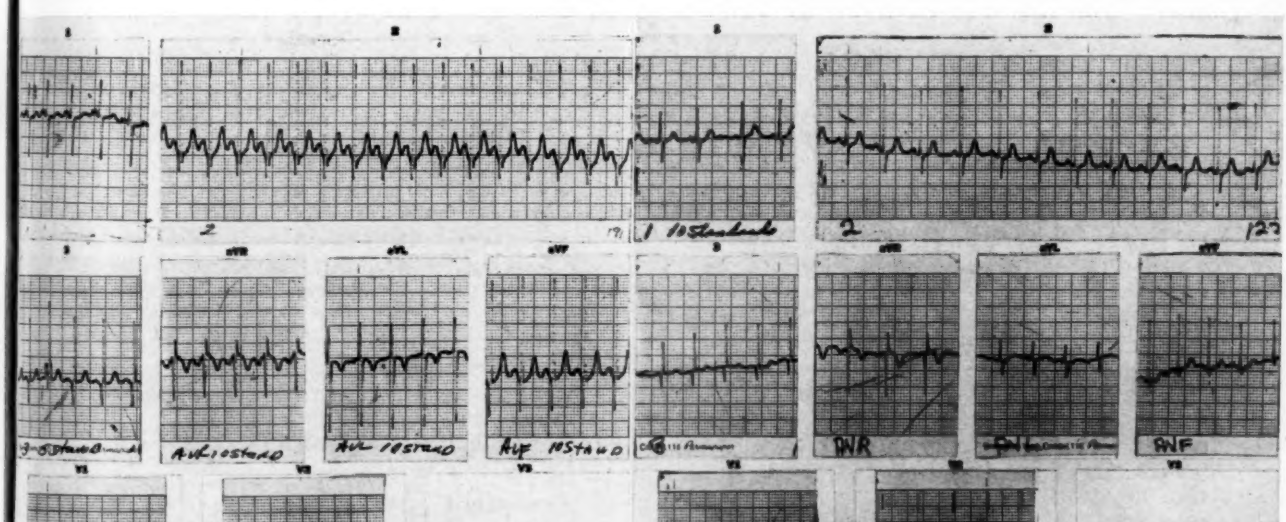

Fig. *2.* Electrocardiograms of the children. *Left:* Twin A. The P waves are broad and notched in Lead I, tall and broad in Leads II and aV_F. There is marked clockwise rotation in the precordial leads. The deep S waves in the left ventricular leads suggest right ventricular hypertrophy. This impression is strengthened by the occurrence of a normal left precordial pattern in the ECG of the unaffected twin (*right*).

Case reports

Endocardial fibroelastosis in one of monozygotic twins

Harold E. Stadler, M.D.
Indianapolis, Ind.

Disparity in the cardiac status of monozygotic twins has been reported in the past, with a different lesion being present in the two instances.[1,2] The present report concerns a third lesion observed in one of "identical" twins. Fortunately, the babies under discussion were closely observed shortly after birth, and the details of their physical appearance carefully noted. The placental structure was also described in detail. The importance of this data became evident when the ravages of a disease process resulted in a loss of the close resemblance.

Dr. James Hawk, who delivered the infants, wrote as follows: "It was known that this patient was larger than average for the estimated gestation; however, I had not been able to hear two fetal hearts even though I suspected a multiple pregnancy. The patient refused to have an x-ray made. Labor occurred two weeks early and both babies reacted well, the first one being somewhat smaller than the second. The mother was Rh-negative, so cord blood from each infant was sent to the laboratory. Examination of the placentas revealed that they were fused and that there was only one chorion but two amnions and that portions of the membranes separating the babies were very thin and seemed to be in only two layers."

Baby A weighed 4 pounds and 2 ounces, and Baby B weighed exactly 1 pound more (5 pounds and 2 ounces). Examination of the two infants was entirely negative, and they appeared to be identical. The blood groups were found to be the same: blood group A, Rh subtypes C, D, and E negative. The anti-M, anti-N, c, and e were positive. The Coombs test was negative in both instances, and routine blood counts were within normal limits. The smaller infant gained well and was dismissed at the age of 3 weeks, at which time his weight was 5 pounds and 9 ounces. He was said to have weighed 8 pounds at the age of 6 weeks.

The infants were not observed again until Nov. 19, 1959, at which time (age 16 months) there was a striking difference in the appearance of the twins. Twin A weighed 19¼ pounds and was 30 inches long. Air hunger was evident, with a grunt on expiration, retraction of the intercostal spaces and episternal notch on inspiration, and an ashen-gray color of the skin. There was no clubbing of the fingers or toes. The heart was enlarged in all diameters, and there was a thrill particularly marked at the apex. The rhythm was regular, but the rate was quite consistently 160 per minute. A generalized harsh systolic murmur was most prominent at the mitral area. The rapid rate precluded definition of gallop rhythm. The breath sounds were subdued over the bases of the lungs, and showers of fine moist râles could be heard. Hepatosplenomegaly was not present, and there was no peripheral edema.

Twin A was said to have never thrived as well as his sibling. Pallor had been present since the age of 4 months. Four days prior to this examination, he had become anorexic and had developed an expiratory grunt which was quite progressive in nature. Cough had been moderate, but restlessness and irritability had been severe.

Twin B at this time weighed 22½ pounds and was 31½ inches in length. He showed no defect except for intense pallor of the skin and mucous membranes. His hemoglobin was found to be 7.8 Gm. per hundred cubic centimeters of blood.

Twin A was hospitalized on Nov. 13, 1959. The hemoglobin was 7 Gm. (hematocrit, 29); the leukocyte count was 8,900 with normal differential.

From the Department of Pediatrics, The Community Hospital, Indianapolis, Ind.
Received for publication May 26, 1960.

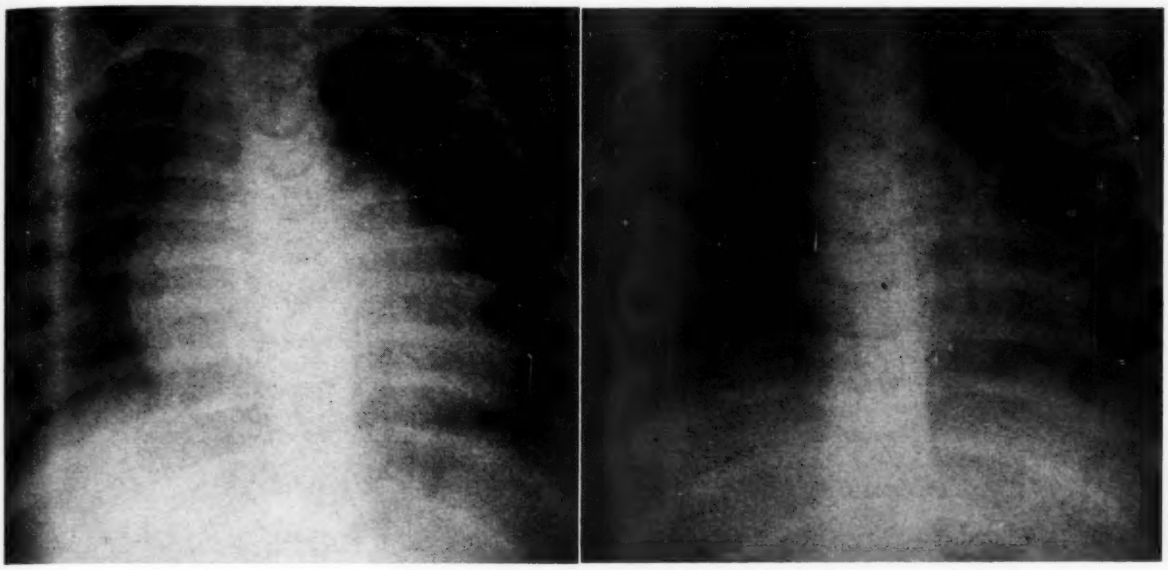

Fig. *1*. Radiograms of the chests of the twins, showing marked enlargement of the heart of the affected child. *Left:* Twin A. *Right:* Twin B.

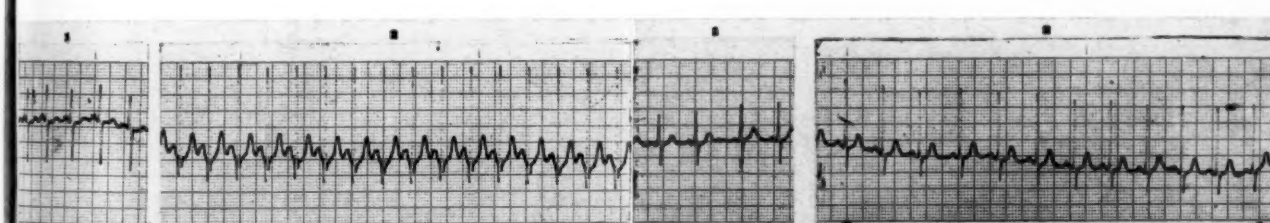

Fig. *2*. Electrocardiograms of the children. *Left:* Twin A. The P waves are broad and notched in Lead I, tall and broad in Leads II and aV_F. There is marked clockwise rotation in the precordial leads. The deep S waves in the left ventricular leads suggest right ventricular hypertrophy. This impression is strengthened by the occurrence of a normal left precordial pattern in the ECG of the unaffected twin (*right*).

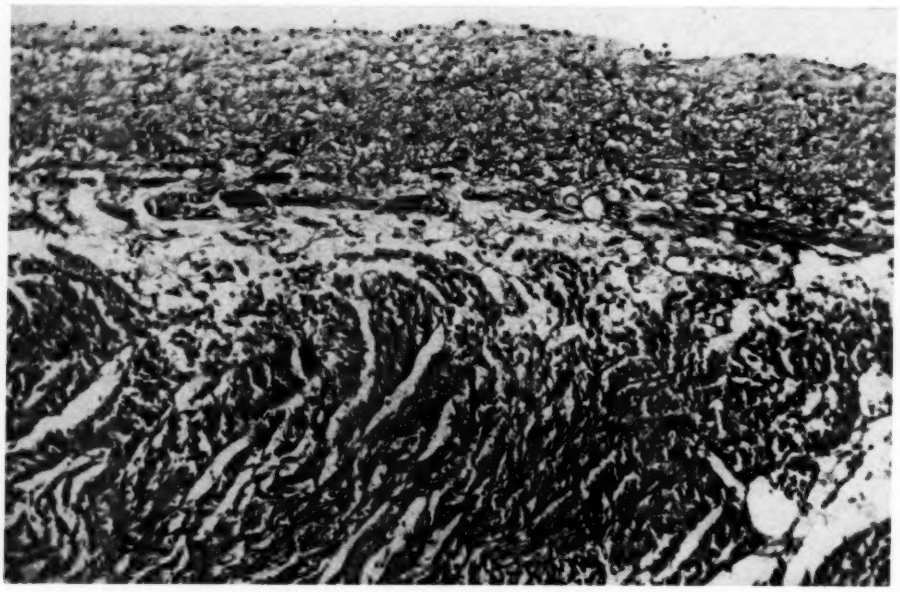

Fig. *3.* The endocardial layer shows marked thickening (magnification ×120; reduced ⅓).

The urine was negative. The chest x-ray film showed generalized cardiac enlargement, with changes at the lung bases indicative of pneumonitis or passive congestion due to cardiac decompensation.

Treatment consisted of Croupette with 6 liters of oxygen per minute, and tetracycline, one teaspoon every 6 hours. The congestive pulmonary findings had regressed by the fifth day, and 125 c.c. of whole blood was given by slow intravenous drip. This was repeated 48 hours later, after which the hemoglobin level was 15 Gm. per hundred cubic centimeters of blood.

Definite diagnosis as to the nature of the cardiac disorder was not made, and the child was dismissed on Nov. 20, 1959. Readmission became necessary on Jan. 7, 1960. A moderate degree of pallor was present, and the hemoglobin was found to be 11.5 Gm. The cardiac findings were those of progressive enlargement of the heart. The carbon-dioxide combining power was 17 mEq./L., and the fasting blood sugar was 104 mg. per cent. Fluoroscopic examination of the chest showed the heart to have enlarged twofold since the previous observation, and the left atrium was strikingly prominent. Endocardial fibroelastosis was suspected.

Oxygen therapy was necessary, and digitoxin, 0.6 mg., was given initially, followed by 0.06 mg. daily. Forty-five milligrams of chlorothiazide was given orally twice daily.

The child was given the above-mentioned medication at home but did not do well and was readmitted to the Community Hospital on Feb. 20, 1960. His weight had dropped to 17½ pounds, and the congestive failure was extreme. Symptomatic care was unavailing, and the patient died on March 18, 1960. Necropsy was limited to the heart.

*Necropsy findings.** The heart was markedly enlarged, with the apex lying in the left mid-axillary line. There was an increased amount of pericardial fluid, and the pericardium was smooth and glistening. All cardiac chambers were dilated, with an increase in thickness of the musculature. The myocardium was firm and reddish-brown. The endocardium over the left ventricle, particularly along the interventricular septum, was thickened and grayish-white. The underlying myocardium could not be seen through the endocardium in many areas. The leaflets of the mitral valve were thickened with leaflets of other valves which showed no abnormal change. The ductus arteriosus was closed.

Multiple sections from the heart showed a moderate thickening of the endocardium. This is consistent with subendocardial fibroelastosis.

Comment

A pathologically proved instance of fibroelastosis of the endocardium in one of monozygotic twins is presented. A search of the literature fails to reveal another such report, although Kempton[3] reported such a situation based upon clinical data. The P-wave changes found are usually not noted in the electrocardiogram of patients with endocardial fibroelastosis, yet must reflect the nonspecific factor of auricular enlargement. Low voltage and conduction disturbances are unusual, but the conduction disturbance has been reported[4] in one infant. The early onset of the disease suggests a congenital origin of it, yet the occurrence in one of

*Dr. Ray Schmoyer performed the autopsy.

monozygotic twins (and an isolated instance in one family) gives no information as to any genetic factor in its origin. The surviving twin will be observed closely since it is possible that he may show evidence of the disorder with the passage of time.

The photographic work was done by Mr. Robert Albright, Indianapolis, Ind.

REFERENCES

1. Stadler, H. E.: Disparity in the cardiac status of monozygotic twins, J. Pediat. **47**:353, 1955.
2. Stadler, H. E., and Chroniak, W.: Discordant monozygotic twins, J. Pediat. **49**:450, 1956.
3. Kempton, J. J.: Endocardial fibroelastosis in one of 3-year-old twins. Review 6 years later, Proc. Roy. Soc. Med. **52**:643, 1959.
4. Stadler, H. E., Reid, C. A., and Friedman, H. P.: Prenatal fibroelastosis ("fetal endocarditis") mainfested clinically by total heart block, J. Pediat. **36**:370, 1950.

Traumatic aortico–right atrial fistula: Report of a case corrected by operation

A. Swanepoel, M.B., M.R.C.P.
V. Schrire, M.B., M.Sc., Ph.D., M.R.C.P.
M. Nellen, M.D., M.R.C.P.
L. Vogelpoel, M.D., M.R.C.P.
C. Barnard, M.D., M. Med., M.S., Ph.D.
Cape Town, South Africa

Acquired fistulous communications between the aorta and right chambers of the heart are uncommon. The majority occur spontaneously at the level of the sinuses of Valsalva, which have undergone aneurysmal dilatation and ruptured into the atrium, ventricle, or pulmonary artery. Traumatic communications very rarely permit a sufficient period of survival for the observation of hemodynamic sequelae and for appropriate treatment. It is for these reasons that the following case is presented.

Case report

W. B., a 30-year-old male Bantu, was admitted elsewhere on May 22, 1959, after having been stabbed through the third intercostal space to the right of the sternum some hours previously. His general condition was satisfactory, and an x-ray film of his chest showed a small amount of air and fluid in the right hemithorax. On May 26, he became acutely dyspneic, but improved after the aspiration of 800 ml. of altered blood from the right hemithorax. The following day he went into shock quite suddenly, his blood pressure was unrecordable, and because further bleeding was suspected, a thoracotomy was performed. A severed right internal mammary artery was transfixed and tied, 3 pints of blood were removed from the right pleural cavity, and a 1-cm. cut was identified in the anterior aspect of the pericardium overlying the right atrium. The pericardial sac was opened and a small amount of blood was aspirated, whereupon a linear wound, 1 cm. in length, adjacent to and parallel with the atrioventricular groove was found to be bleeding profusely. A coarse systolic thrill over the right atrium suggested intracardiac pathology, but in the absence of suitable facilities, a cardiotomy could not be performed. The atrial stab wound was closed with 2-O silk sutures.

Some hours later, pulsatile distention of his neck veins and a loud left parasternal systolic murmur were noticed. Digoxin and mersalyl were given, with some resultant improvement, although the venous distention and murmurs persisted. On June 9, he was seen at the Cardiac Clinic, Groote Schuur Hospital. The striking signs now were grossly distended jugular veins and enlargement of the liver to 8 cm. below the costal margin; both veins and liver showed marked expansile systolic pulsation. No edema or dyspnea were noted, and the pulse appeared to be normal, having no collapsing tendency. The blood pressure was 120 70 mm. Hg. The mediastinum and cardiac apex were displaced toward the left. To the right of the sternum a loud fistulous murmur could be heard enveloping the second sound, whereas a pansystolic murmur followed by a loud early diastolic filling sound were present in the third and fourth left intercostal spaces (Fig. 1). The rest of the examination was not contributory.

The chest radiograph (Fig. 2,*A*) showed a large collection of fluid in the right hemithorax and considerable cardiac enlargement. Left lung appeared normal; no evidence of vascular engorgement.

From the Cardiac Clinic, Groote Schuur Hospital, and the Departments of Medicine and Surgery, University of Cape Town, Cape Town, South Africa.
This study was supported by a grant from the Council for Scientific and Industrial Research and the City Council of Cape Town.
Received for publication June 29, 1960.

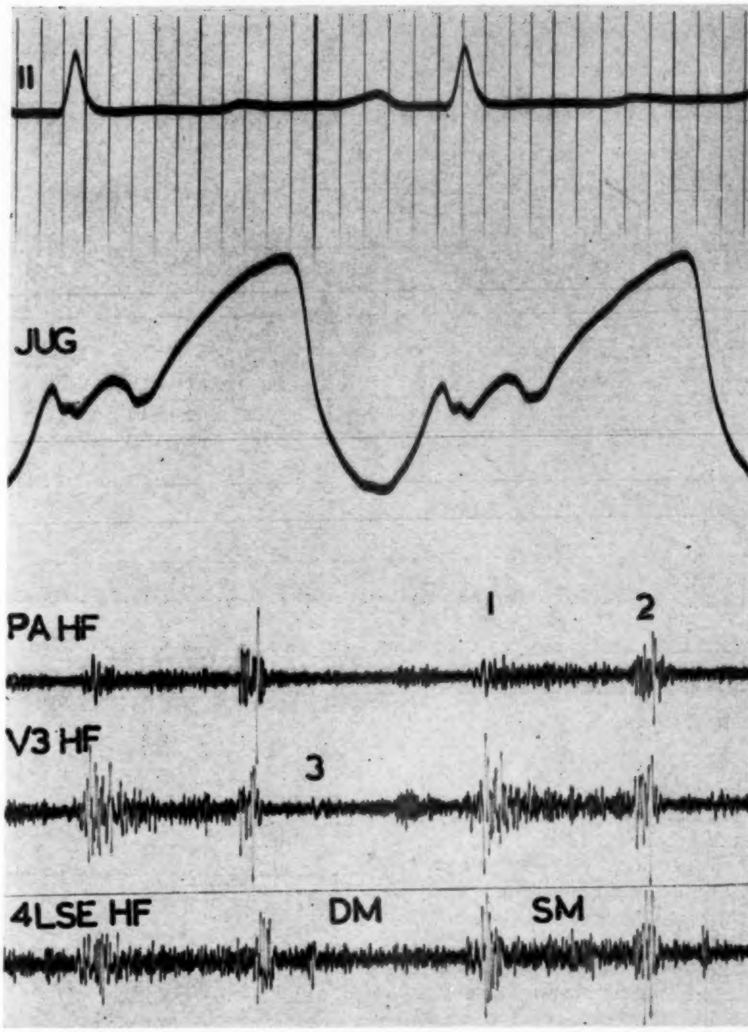

Fig. *1.* Preoperative phonocardiogram, with accompanying jugular venous pulse tracing. *HF:* High frequency. *PA:* Pulmonary artery. *V3:* V3 position on anterior chest wall. *4LSE:* Fourth intercostal space, left sternal edge (not recorded synchronously). The continuous murmur is best shown in the *4LSE* tracing; a third sound is seen at the *V3* position, and an atrial systolic murmur at *V3* and *PA*. The jugular tracing shows the partially fused CV waves suggestive of severe tricuspid incompetence.

The electrocardiogram showed sinus rhythm, P-R interval of 0.18 second, vertical axis (circa 85°), and widespread T inversion which was more pronounced in the right precordial leads but no evidence of right ventricular strain (Fig. 3,*A*).

Cardiac catheterization was performed on July 1, 1959. The samples of blood showed a 4.2 L./min. left-to-right shunt at the right atrial level (see Table I). Pressure tracings recorded from the right atrium showed a very pronounced Y descent, followed by a steep presystolic A wave, a restriction of the X descent, and partially fused C and V waves (Fig. 4,*A*). This configuration suggested a reflux into the right atrium during ventricular systole. Elevation of the end-diastolic pressure in the right ventricle was in keeping with failure of this chamber (Fig. 4,*B*).

A preoperative diagnosis of a traumatic fistulous communication between the aorta and right atrium was made. An additional traumatic defect of the tricuspid valve was suspected because of the gross signs of tricuspid incompetence, although it was appreciated that the latter could be mimicked by an aortico-right atrial fistula of sudden onset.

An operation to repair the defect was performed on July 13, via a right anterolateral thoracotomy through the bed of the fifth rib. The right atrium was much enlarged, and a continuous thrill could be palpated over it. Under cardiac bypass,[1] the aorta was cross-clamped and the right atrium was opened to reveal a defect about 1 cm. in diameter between the right atrium and the root of the aorta.

No associated defects were found on close inspection of the tricuspid valve and right ventricle.

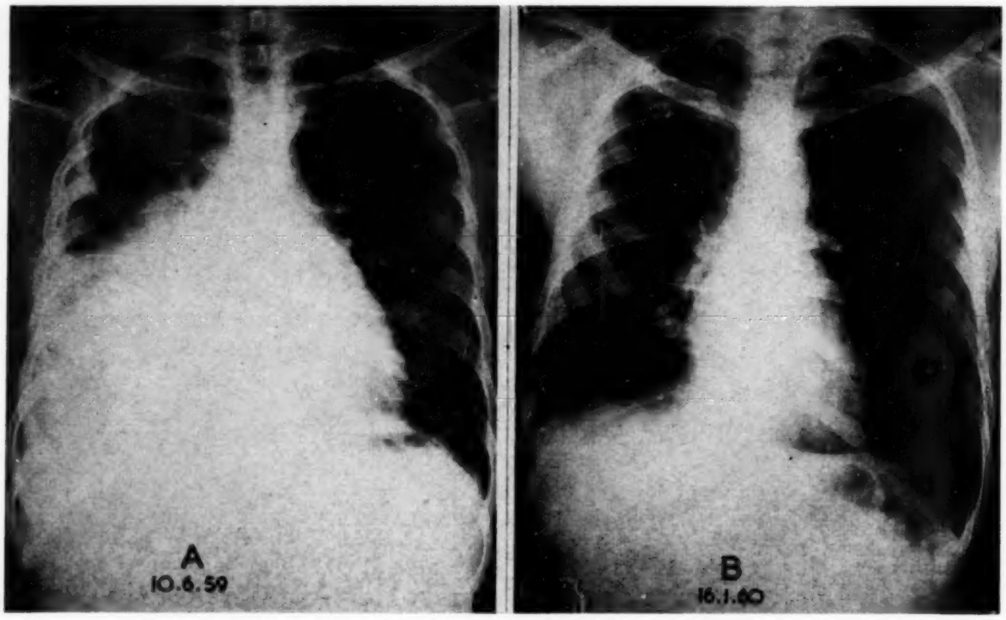

Fig. 2. *A*, Preoperative chest radiograph, showing right pleural effusion and cardiac enlargement. *B*, Postoperative radiograph, showing restoration of normal cardiac silhouette.

With intermittent aortic occlusion, the fistula was closed by means of interrupted 3-O mattress sutures, which were subsequently tied over an Ivalon pledget, thus sealing the breach securely. The atrium was then closed with 3-O silk sutures. The total period of perfusion was 39 minutes. Sinus rhythm with occasional ectopic beats had persisted throughout the procedure, and the electroencephalogram remained normal. The patient's recovery following the operation was dramatic; a striking feature was the almost immediate disappearance of all signs of tricuspid incompetence and a rapid return of the liver to normal.

Clinical support for complete closure of the defect was inferred from the absence of any residual murmurs or signs of tricuspid incompetence. The patient left the hospital on the twenty-second postoperative day and soon returned to work. Six months later, no abnormal signs were elicited; the chest radiograph was normal (Fig. 2,*B*). The electrocardiogram showed increased voltage and slight slurring of the terminal QRS complex (Fig. 3,*B*), probably a normal variant.

Table I. *Cardiac catheterization*

Site	*Pressure (mm. Hg)*	*Oxygen saturation (%)*
High SVC		44
Low SVC		48
High RA	15/2 (Mean 10.5)	75
Mid RA		79
Orifice of IVC		68
RV	30/0–10	75
MPA	22/14	76
RBA	100/62	93

Systemic flow: 6.7 L./min.
Pulmonary flow: 10.9 L./min.
Left-to-right shunt: 4.2 L./min.
Pulmonary vascular resistance: 1.4 units

Comment

Acquired communications between the aorta and right-sided heart chambers constitute a grave threat to cardiac function; the duration of life depends on the size and site of the shunt. Our knowledge of the natural history of this sequence of events is derived largely from descriptions of cases of rupture of the sinuses of Valsalva. Aneurysms at this site are most frequently due to congenital weakness, but may also be the result of acquired pathology, such as syphilitic or mycotic aortitis. Uncomplicated aneurysms are not attended by signs or symptoms in the great majority of cases.[2,3] However, their rupture is accompanied by a distinctive clinical constellation, which was fully described by Thurnam,[4] in 1840, and more recently by Maud Abbott,[5] in 1919, and which frequently permits the timing of this event to be accurately established. Thus, analysis of 37 cases of ruptured sinuses reported in the literature up to

1957, indicated a mean survival time of 3.9 years following rupture. If 2 patients who lived for 10 and 15 years are excluded, this mean drops to 1 year[6]; death in the majority of cases was due to cardiac failure, and in a minority to bacterial endocarditis. The chamber into which a sinus ruptures has some bearing on the symptomatology. A defect between the aorta and pulmonary artery simulates an acute form of patent ductus arteriosus, and because the lungs and left heart are immediately involved, severe symptoms generally ensue and lead to death within days or weeks.[7] Rupture of the aorta into the right ventricle has similar effects, but provided that other vital structures, such as junctional tissue and coronary vessels, remain intact, the outlook improves when the break occurs more proximally between the aorta and the right atrium or superior vena cava.[7] The latter two structures dilate, and thus partially dissipate the kinetic energy and volume effect of an influx of arterialized blood under high pressure, thereby relieving the strain on the pulmonary circuit and left heart. However, signs of systemic venous engorgement may then be more pronounced, as in our patient, and the systolic influx of blood into the right atrium may produce hemodynamic signs very similar to those of tricuspid incompetence. Rupture of the root of the aorta into the right ventricle, with resultant right ventricular failure and functional tricuspid incompetence, may produce clinical signs indistinguishable from those of aortico-right atrial fistula; and since some arterialization may then be encountered at the atrial level, cardiac catheterization may also be misleading. The tricuspid valve may itself

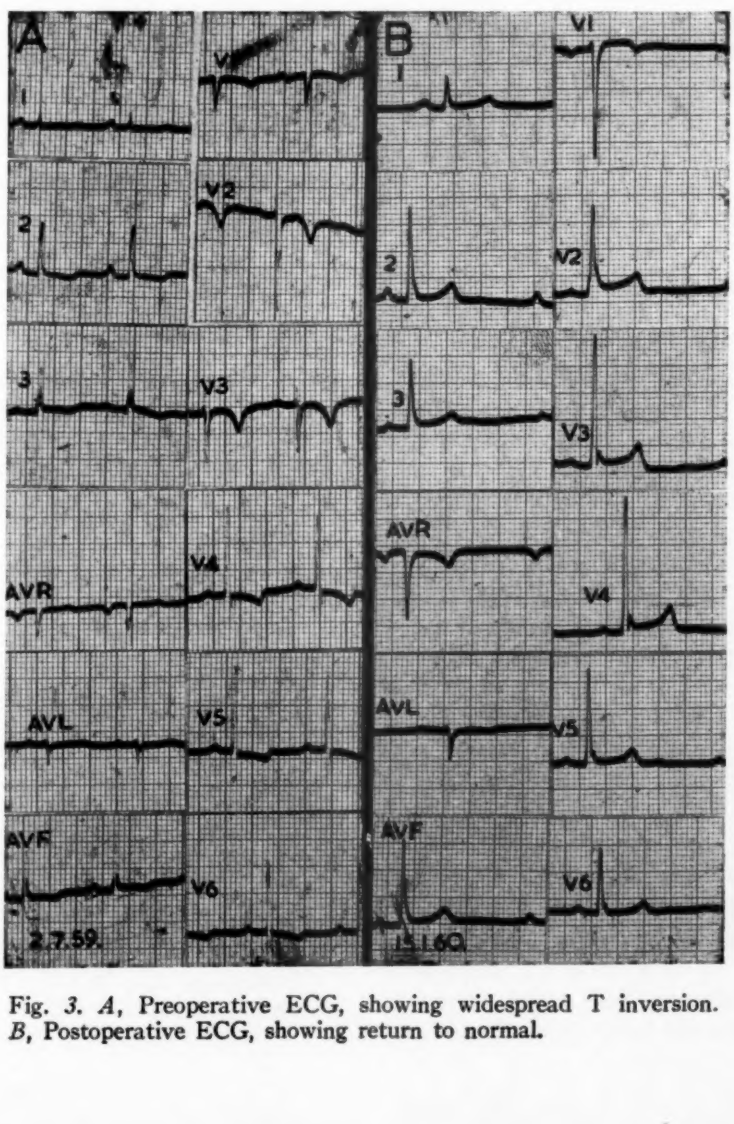

Fig. 3. *A*, Preoperative ECG, showing widespread T inversion. *B*, Postoperative ECG, showing return to normal.

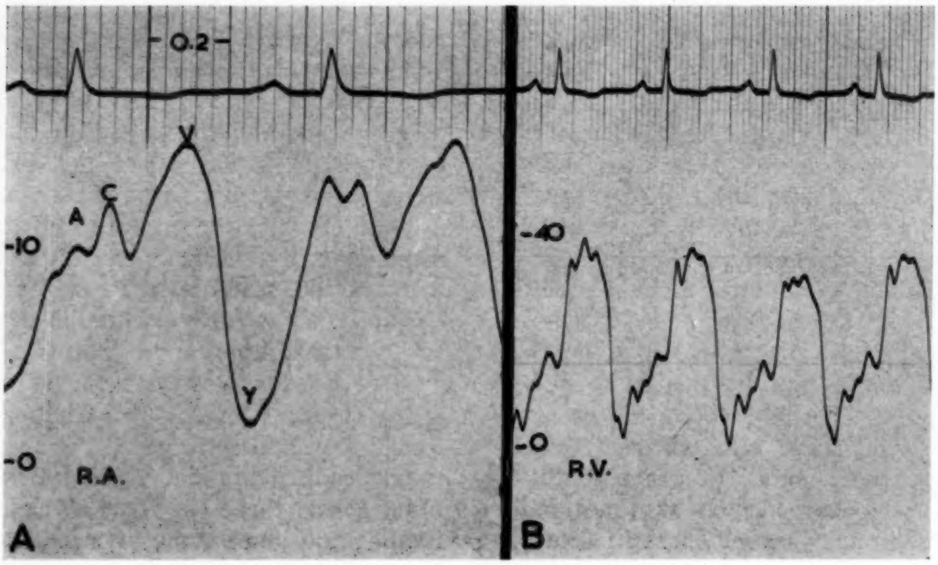

Fig. *4*. *A*, Right atrial pressure tracing. The large systolic wave composed of partially fused A, C, and V waves suggests tricuspid incompetence. *B*, Right ventricular pressure tracing. The elevated end-diastolic pressure suggests a failing chamber.

be deformed by the aneurysm, or damaged in traumatic cases, with resultant tricuspid incompetence.

Thus, three possible mechanisms may be associated with the dynamic changes of tricuspid incompetence, and the methods described above are clearly inadequate to distinguish which is operative in a given case. The fistulous murmur is likely to obscure any possibly associated murmur of tricuspid incompetence, and the dynamic effects of tricuspid incompetence, as reflected in the jugular veins and right atrial pressure tracings, may be closely simulated by a leak from the aorta into the right atrium. When indicated, the use of dye-dilution and cineangiocardiographic techniques may provide the answer, although final diagnosis may usually be deferred until atriotomy. Correction by operation is clearly indicated whenever possible, in view of the grave prognosis of untreated cases, and reports of successful repair are appearing with increasing frequency.[8-10]

The foregoing observations can only infrequently be related to cases of traumatic aortico-right heart fistulas. Such lesions are generally rapidly fatal, but occasionally, as in our case, a prompt operation may remove the danger associated with the external heart wound, while leaving an intracardiac shunt which can later be dealt with in definitive fashion. A few reports of repaired traumatic aortico-right ventricular fistulas have already appeared.[11-13] In the available literature no other example of successful surgical repair of traumatic aortico-right atrial fistula could be found.

Conclusions

A case of traumatic aortico-right atrial fistula caused by a stab wound in the chest is described. Right heart failure rapidly developed and promptly regressed following successful open-heart closure of the defect.

We wish to thank Dr. A. Landau and Dr. R. Hewitson for referring the case for study and treatment, and the Superintendent, Dr. J. Burger, for permission to publish. We should also like to acknowledge the assistance received from our technicians Mr. L. W. Piller and Miss S. Joseph.

REFERENCES

1. Barnard, C. N., Phillips, W. L., deVilliers, D. R., Casserley, R. D., Hewitson, R. P., van der Riet, R. L., and McKenzie, M. B.: Some experiences with intracardiac surgery using the helix-reservoir bubble oxygenator with total cardiopulmonary bypass, South African M. J. **33**:789, 1959.
2. Jones, A. M., and Langley, F. A.: Aortic sinus aneurysms, Brit. Heart J. **11**:325, 1949.
3. Oram, S., and East, T.: Rupture of aneurysm of aortic sinus (of Valsalva) Into the right

side of the heart, Brit. Heart J. **17**:541, 1955.
4. Thurnam, J.: Med-Chir. Trans. **23**:323, 1840. Cited by Oram and East.[3]
5. Abbott, M. E.: Contributions to medical and biological research. Sir William Osler Memorial. P. B. Hoeker. **2**:899, 1919. Cited by Sawyers, Adams and Scott.[6]
6. Sawyers, J. H., Adams, J. E., and Scott, H. W.: Surgical treatment for aneurysms of the aortic sinuses with aortico-atrial fistula, Surgery **41**:26, 1957.
7. Herrmann, G. R., and Schofield, N. D.: The syndrome of rupture of aortic root or sinus of Valsalva into the right atrium Am. Heart J. **34**:87, 1947.
8. Morrow, A. B., Baker, R. B., Hanson, H. E., and Mattingly, T. W.: Successful surgical repair of a ruptured aneurysm of the sinus of valsalva, Circulation **16**:533, 1957.
9. Kay, J. H., Anderson, R. M., Lewis, R. L., and Reinberg, M.: Successful repair of sinus of Valsalva-left atrial fistula, Circulation **20**:427, 1959.
10. Lillehei, W. B., Stanley, P., and Varco, R.: Surgical treatment of ruptured aneurysms of the sinus of Valsalva, Ann. Surg. **146**:459, 1957.
11. Smyth, N. P. D., Adkins, P. D., Kelser, G. A., and Catalayud, J.: Traumatic aortic-right ventricular fistula, Surg. Gynec. & Obst. **109**:566, 1959.
12. King, H., and Shumacker, H. B.: Surgical repair of a traumatic aortic-right ventricular fistula, J. Thoracic Surg. **35**:734, 1958.
13. Morris, G. C., Foster, R. P., Dunn, J. R., and Cooley, N. M.: Traumatic aortico-ventricular fistula; report of two cases successfully treated, Am. Surgeon **24**:883, 1958. Cited by Smyth, et al.[11]

Clinical pathologic conference

B. M. Gasul, M.D.
R. F. Buenger, M.D.
O. C. Julian, M.D.
*R. E. Trueheart, M.D.**
Chicago, Ill.

Clinical review

First Admission (April 7, 1959 to April 10, 1959). This 7½-year-old white boy was admitted to Presbyterian-St. Luke's Hospital on April 7, 1959, with a history of a known heart murmur and a precordial bulge since birth. The heart murmur was discovered immediately following a normal delivery; there was not then nor had there ever been cyanosis. He had always been active and there was no limitation of activity, although his mother noticed some dyspnea on strenuous exertion, such as running up a flight of stairs. There was no history of squatting, orthopnea, ankle edema, syncope, hypertension, or chest pain.

PHYSICAL EXAMINATION. The blood pressure was 110/68 mm. Hg in the left arm, and 114/72 in the right arm. The pulse was 84 per minute and regular. The child appeared to be within the lower limits of development for the stated age. The tonsils were enlarged but not inflamed. The lungs were clear. There was a marked precordial bulge. The cardiac apex was in the anterior axillary line at about the fifth or sixth left intercostal space. On auscultation the first heart sound at the apex was loud. The second heart sound was not audible at the apex. At the base the first heart sound was not audible. The second heart sound was loud and lightly split and more prominent to the left of the sternum. There was a very loud crescendo-decrescendo systolic murmur occupying the entire systolic phase, audible throughout the precordium but loudest in the second and third left intercostal spaces. In the same area there was a loud, rumbling diastolic murmur, decrescendo in character. The peripheral pulses, including the femorals, were bilaterally strong and regular. There was no clubbing, venous distention, or edema.

LABORATORY DATA. The hematocrit was 40; hemoglobin, 13.6 Gm. per cent; white blood cell count, 6,450, showing 42 per cent lymphocytes, 54 per cent neutrophils, 4 per cent bands, 2 per cent monocytes. The urinalysis was normal. The Hanger test was negative; thymol turbidity was 3.9 units. The serology was negative. The electrocardiogram was interpreted as showing right heart strain and suggesting right ventricular hypertrophy. Cardiac fluoroscopy and chest x-ray films showed cardiac enlargement, probably right ventricular. There was vigorous pulsation of the enlarged pulmonary arteries which was greater on the left. The right pulmonary artery appeared much less enlarged. The lungs were undervascularized. There was difficulty in entering the pulmonary artery on cardiac catheterization. The results of catheterization are shown in Table I.

Second Admission (May 7, 1959 to May 13, 1959). The patient was readmitted on May 7, 1959, for further study and treatment.

PHYSICAL EXAMINATION. The blood pressures (mm. Hg) were: right arm, 115/70, left arm, 115/80,

Table I. *Catheterization findings*

Position of the catheter	*Oxygen content (vol. %)*	*Pressure (mm. Hg)*
Superior vena cava	12.65	2/0
Upper right atrium	12.64	2/0
Middle right atrium	12.13	2/0
Lower right atrium	12.11	
Inferior vena cava	10.15	
Right ventricle, inflow tract	13.01	75/0
Right ventricle, outflow tract	13.50	75/0
Main pulmonary artery	12.79	25/8
Left pulmonary artery	13.06	25/8
Right pulmonary artery	13.15	25/8
Femoral artery	15.92	70/50
Capacity	16.72	
Saturation	95.2%	

From the Presbyterian-St. Luke's Hospital, Chicago, Ill.
Received for publication Feb. 26, 1960.
*Present address: Evanston Hospital Association, Evanston, Ill.

right leg, 128/80. The pulse was 100 and regular. The chest was clear. Forceful Grade 4 systolic and Grade 2 diastolic thrills were present over the entire precordium, particularly at the left sternal border at the fourth intercostal space. The systolic thrill was present in the neck. There was a Grade 5 harsh, systolic murmur at the left sternal border in the fourth intercostal space, which was transmitted to the back, entire chest, below the diaphragm, neck, and arms to the elbows. A loud diastolic murmur was heard over the same area and transmitted to the entire precordium and between the scapulae. This diastolic murmur was rough and not blowing. There was no edema, cyanosis, or unusual peripheral vascular findings.

LABORATORY DATA. The hemoglobin was 12.7 Gm. per cent; white blood cell count, 6,400, showing 73 per cent neutrophils, 2 per cent bands, 24 per cent lymphocytes, and 1 per cent eosinophils. The urinalysis was negative. A chest x-ray film showed the heart to be enlarged to the left, and there was a marked increase in the size of the pulmonary arteries. There was an increase in the vascularity of the lungs, with the exception of the right lower lobe. A venous angiogram demonstrated a large right ventricle and large pulmonary arteries. There was a blanching of the right ventricular contrast by a shunt. No infundibular or pulmonary valvular stenosis was identified. The aorta was small and dextroposed and displaced anteriorly. An electrocardiogram was thought to be compatible with right ventricular hypertrophy, possibly combined with left ventricular hypertrophy, with right ventricular hypertrophy predominant.

HOSPITAL COURSE. On May 12, the patient underwent a reparative operation with cardiopulmonary bypass. Postoperatively, the patient bled considerably and went into shock, necessitating several transfusions. He was reopened but no actual point of bleeding could be found. Numerous oozing points were stopped and the chest was closed again. After that episode the patient went into cardiac arrest about 1½ hours after the second operation. The chest was opened, the heart massaged, and with supportive therapy the heart was brought back to normal sinus rhythm. About a half hour after the chest was closed the patient went again into cardiac standstill and expired.

Discussion

DR. GASUL: On the basis of the history of this 7½-year-old white boy, I may state that this patient had a noncyanotic type of congenital malformation of the heart. I can definitely exclude all serious forms of the cyanotic types of congenital malformation with the following exceptions: mild, clinically noncyanotic type of tetralogy of Fallot; anomalous entrance of all pulmonary veins into the supracardiac area with an atrial septal defect; truncus communis with large pulmonary arteries and mild forms of anatomic Eisenmenger complex. Although patients with the conditions just mentioned almost always reveal some peripheral arterial oxygen unsaturation, they may appear clinically as belonging to the noncyanotic type. The arterial oxygen unsaturation is often not recognized clinically until it is below 80 per cent or even lower.

On the basis of the physical examination and conventional laboratory tests, we can state the following: the heart is definitely enlarged; it is in the fifth or sixth left intercostal space in the anterior axillary line, and the presence of a precordial bulge usually signifies right ventricular hypertrophy; the normal femoral pulses and the normal blood pressures exclude a coarctation of the aorta; the very loud pansystolic murmur, maximal at the second and third left intercostal spaces, signifies the presence of a ventricular septal defect. This murmur obliterates the first heart sound at the base and the second heart sound at the apex. This proves that the murmur is pansystolic and differentiates it from a loud ejection systolic murmur due to pulmonary and/or aortic valvular stenosis, because the latter starts after the first heart sound and ends before the closure of the involved valve. The second heart sound at the base is reported to be loud and lightly split. It is of the utmost importance to analyze this second sound. Does the "lightly split" mean a single sound, or that the second component (the pulmonic closure) of the second sound is diminished in intensity?

In tetralogy of Fallot the second sound at the base is usually single and loud because only the closure of the aortic valve is heard at this area. There usually is no splitting of the second sound at the pulmonary area because an insufficient amount of blood enters the pulmonary vessels under the lower-than-normal pressure. In mild cases of tetralogy of Fallot one may hear the closure of the pulmonary valve because the stenosis is not marked and a greater amount of blood enters the pulmonary artery. But even in these mild cases the pulmonary component of the second sound is diminished in intensity and is delayed. Therefore, the statement in the protocol that the second sound is loud and lightly split most probably means that it was single. It was certainly not delayed.

We can exclude the presence of valvular pulmonary stenosis with a normal aortic

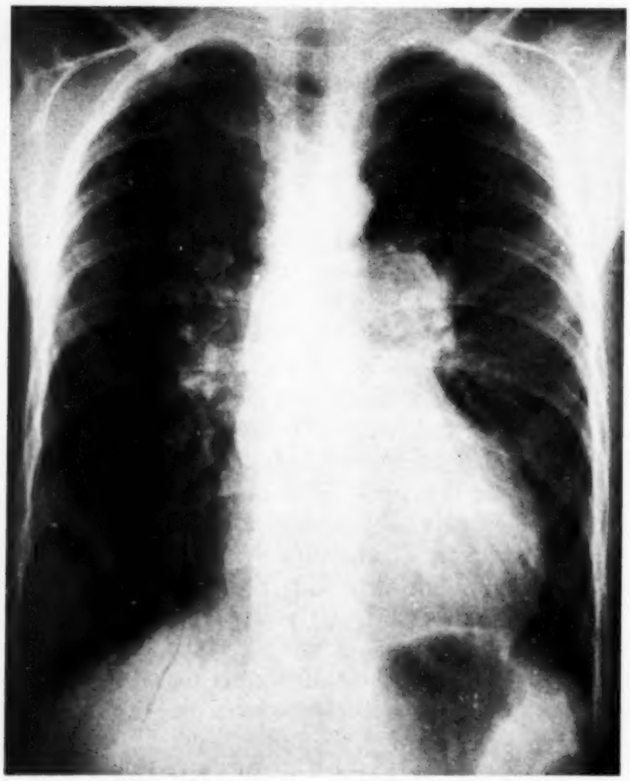

Fig. *1*. Posteroanterior chest radiograph, showing large pulmonary arteries, moderately enlarged heart, and translucent right lower lobe.

root, i.e., isolated pulmonary stenosis, because of the pansystolic murmur and a single loud second sound at the pulmonary area. In isolated pulmonary stenosis, one hears an ejection type of systolic murmur which begins after the first heart sound and ends before the closure of the pulmonic component of the second sound. This pulmonic component is always delayed, and diminished in intensity, so that one, therefore, hears a weak second sound. In the vast majority of all these patients a high-frequency systolic click is heard following the first heart sound, and we believe that this early systolic click is a result of the opening of the stenosed and thickened pulmonary valve. Its pathogenesis is similar to the opening snap of the stenosed mitral valve that one hears in mitral stenosis. In extremely severe cases of isolated pulmonary stenosis with practically no movements of these cusps, this early click is, as would be expected, not heard. In some of these patients the pulmonary component of the second sound also cannot be heard, although the phonocardiogram will usually show this markedly delayed and low-intensity pulmonic closure. However, these patients with severe isolated pulmonary stenosis still have an ejection type of systolic murmur and they are usually definitely cyanotic, either because of a right-to-left shunt at the atrial level (through the foramen ovale or atrial septal defect) or because of a marked increase in peripheral arteriovenous oxygen difference.

The presence of a loud, rumbling diastolic murmur in the second and third left intercostal spaces presents a real diagnostic problem because one does not hear this murmur in either tetralogies or in isolated pulmonary stenosis. I shall comment on this later.

Examination of the roentgenograms (Figs. 1 and 2) reveals enlargement of the right ventricle and no enlargement of the left atrium, and the pulmonary arteries, especially the left one, are markedly enlarged and pulsate vigorously on fluoroscopic examination. The lungs, particularly on the right side, are undervascularized.

I would now like to see these roentgenograms and to hear Dr. Buenger's interpretation.

DR. BUENGER: The significant findings in the angiocardiogram (Fig. 3) are confined

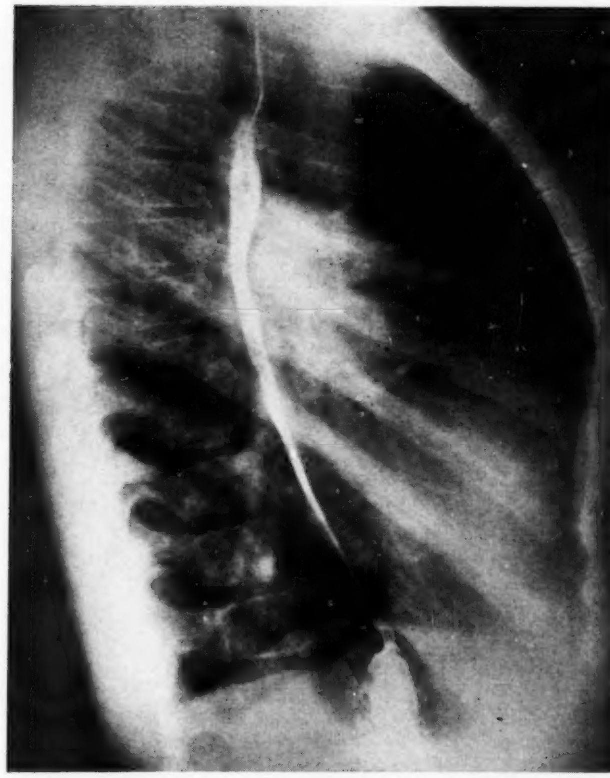

Fig. 2. Lateral chest radiograph, showing marked right ventricular hypertrophy and absence of left atrial enlargement.

to the right side of the heart. There is a blanching of the outflow tract due to a left-to-right shunt. Because of this, the size of the infundibulum is not discerned, but the area just below the pulmonary valve does not appear to be stenosed. The pulmonary valve cusps are never visualized. There is no valvular stenosis. The main pulmonary artery is very large, as is the left main branch. The right pulmonary artery is large but not markedly so. There is a very striking lack of vascularization of the right lower lobe, but the pulmonary artery trunks leading to it appear no smaller than those leading to the other lobes of both lungs. This suggests a localized vascular stenosis or marked lobular emphysema. The rest of the lung appears to have normal vascularity.

DR. GASUL: The electrocardiogram which I am now examining reveals a right axis deviation. The R in Lead aV_R measures 8 mm., and the R in Lead V_1 is 10 mm. There is a definite S wave present in Lead V_2. This is an adaptation type of right ventricular hypertrophy, and it signifies that the pressure in the right ventricle is not higher than that in the left ventricle. If the pressure in the right ventricle is higher than that in the left ventricle, as occurs in severe, isolated pulmonary stenosis, the electrocardiogram often shows the barrage or systolic overfilling type of right ventricular hypertrophy. I like the term "adaptation type of right ventricular hypertrophy" because this clearly defines that in the presence of an associated ventricular septal defect the right ventricle "adapts itself" to the pulmonary stenosis and sends some blood through the "hole" in the septum into the aorta. In severe, isolated pulmonary stenosis the right ventricle has no other outlet and must empty its contents through the stenosed area only, into the pulmonary circulation.

Cardiac catheterization confirms the presence of a right-to-left shunt at the ventricular level and the presence of pulmonary stenosis. The report does not state whether there was infundibular and/or valvular stenosis present. The pressure in the right ventricle is 75/0 mm. Hg, and in the pulmonary artery, 25/8 mm. Hg. The pressure in the femoral artery is noted to be

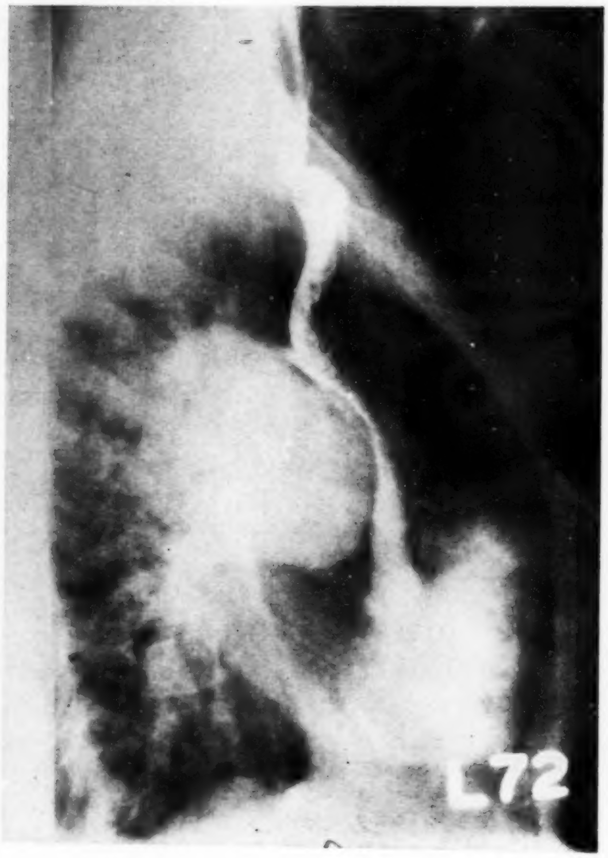

Fig. 3. Lateral angiocardiogram at 1-1/16 second, showing blanching of right ventricle due to left-to-right shunt, lack of visible infundibular stenosis, nonvisible pulmonary valve leaflets, and tremendously dilated pulmonary arteries.

70/50 mm. Hg, and yet the pressures in the arms on two different occasions were 110/68 and 115/70 mm. Hg. Evidently the pressures in the arms, in the femoral artery, and in the right ventricle were not taken simultaneously, but even at that, these findings confirm the well-known fact that the pressure in the right ventricle approximates that in the left ventricle in patients with pulmonary stenosis and large ventricular septal defects and cannot be considerably higher than that in the systemic circulation.

As a result of all these findings, we can now definitely state that the patient has a ventricular septal defect and either infundibular or (and) valvular pulmonary stenosis. One cannot, however, exclude with certainty the presence of only a large ventricular septal defect with marked hypertrophy of the crista supraventricularis without definite infundibular and/or pulmonary stenosis.

The most puzzling findings in this patient are the presence of a rumbling diastolic murmur in the second and third left intercostal spaces and the vigorous pulsations of the enlarged pulmonary arteries in the presence of "undervascularized lungs." This latter condition can be confirmed by the angiocardiographic findings, which, in addition, reveal definite blanching of the outflow tract of the right ventricle due to left-to-right shunt at the ventricular level and some anterior displacement of the ascending aorta.

What can make the pulmonary arteries pulsate in the presence of pulmonary stenosis and insufficient pulmonary blood flow? An associated patent ductus arteriosus or aortic septal defect can be excluded on the basis of the cardiac catheterization findings. I have seen this vigorous pulsation of the pulmonary arteries in a patient who developed pulmonary hypertension a number of years after a Potts operation, but this, also, is not the case here. There remain two other possibilities: absence of the pulmonary valve and/or the presence of stenosis of the branches of the pulmonary arteries. I have seen a number of patients with stenosis or coarctation

Fig. *4*. Right ventricular view, showing absent pulmonary valve, lining of slightly narrowed pulmonary orifice by fibrous ridges, partially removed infundibular muscle mass, and partially closed septal defect.

of the branches of the pulmonary artery which was diagnosed on clinical and conventional laboratory findings, and several cases of tetralogy of Fallot with absent pulmonary valve have been reported in the literature. I have seen the latter at autopsy but have not diagnosed this entity during life.

In summary, I may state the following: the findings here are a large ventricular septal defect and a mild degree of infundibular stenosis, and this usually signifies a noncyanotic type of tetralogy of Fallot. In addition, this patient presents evidence of associated stenosis of the branches of the pulmonary artery, especially of the right branch, and/or absence of the pulmonary valve.

DR. JULIAN: The diagnosis of tetralogy of Fallot was made in this patient at the time of operation. The distribution of the supply of coronary arteries over the surface of the heart and the positioning of the great vessels at the base indicated this diagnosis. The heart was opened, therefore, through the right ventricle, and a very difficult interventricular septal defect was found and repaired. The infundibular stenosis was compensated for by myomectomy, and it was discovered during the operation that the pulmonary valve was represented only by a small, irregular rim of condensed tissue around the valve ring, which was itself approximately normal in size. The postoperative course in this patient was disastrous because of the occurrence of postoperative bleeding. The chest wound was reopened and the diffuse bleeding was controlled. This control was necessary a second time, and during this period, cardiac arrest occurred and necessitated a period of manual systole. The importance of mentioning the manual systole lies in its destructive effect on the intracardiac repairs. We succeeded in resuscitating the heart, but only temporarily. An important clinical point in regard to this patient is that he had a Fallot deformity without peripheral arterial desaturation. The application of surgery in such acyanotic cases of tetralogy of Fal-

Fig. 5. Left ventricular view, showing defect of ventricular septum.

lot is quite different than in cases of pulmonary stenosis.

DR. TRUEHEART: The heart was enlarged. This was due mostly to a tremendous hypertrophy and dilatation of the right ventricle (Fig. 4). The crista had been surgically altered. It was, therefore, difficult to tell how much stenosis of the infundibulum there had been. The pulmonary orifice was somewhat smaller than normal. There was no pulmonic valve. In its place there was a low rim of valve-like tissue. In the right ventricle beneath this rim there was another band of thick, fibroelastic tissue, which, thus, aided in the formation of a separate, small infundibular chamber. The pulmonary trunk and the right and left pulmonary arteries were markedly dilated up to the hili of the lungs, and the wall of the pulmonary trunk was thickened. The secondary branches of both pulmonary arteries were relatively small, as compared to the arteries themselves, but it could not be stated that they were smaller than normal.

The left ventricle was normal in size and thickness. The ventricular septum at its base presented a defect which measured about 1.5 cm. in greatest dimension (Fig. 5). This was covered by a Teflon patch but a residual defect remained. The aorta straddled the interventricular septum, emerging from both ventricles. The various points of surgical intervention related to the cardiopulmonary bypass showed no abnormality. There was 500 c.c. of bloody fluid in each side of the chest cavity. The anterior portions of the right upper and lower lobes showed small infarcts. In addition, microscopically, both lungs showed severe pulmonary edema and hemorrhage, accompanied by inflammatory cells.

In summary, then, the clinical diagnosis made by Dr. Gasul is borne out by the pathologic findings. We are dealing with tetralogy of Fallot with absence of the pulmonary valve. This syndrome and pathologic complex were recently described by Miller, White, and Lev.[1] We do not know the anatomic base of the lack of vascularization of the right lower lobe.

Diagnosis: Acyanotic tetralogy of Fallot with absence of the pulmonary valve

REFERENCE

1. Miller, R. A., White, H., and Lev, M.: Congenital absence of the pulmonary valve: clinical and pathologic syndrome, Circulation **18**:749, 1958.

Annotations

Notes on cardiovascular disease in Africa

As encountered by an American physician on a brief visit to that continent in March and April, 1959

A cardiological tour of several countries in Africa in the spring a year ago was of such great interest to me, and quite possibly to others, that I am submitting this brief account to the Journal.

Invited by the students of the University of Cape Town to spend three weeks there and one week at the Witwatersrand Medical School in Johannesburg, I traversed the length of Africa on the east, stopping in Cairo, Egypt, in Nairobi, Kenya, and in Kampala, Uganda, to visit the hospitals and medical schools, in order to determine the amount of cardiovascular disease in those places. On the way home from Johannesburg, I stopped in Leopoldville in the Belgian Congo and in Brazzaville and Lambaréné (the location of Dr. Schweitzer's hospital), the latter in the Republic of Gabon, formerly a part of French Equatorial Africa.

Through the kindness of many of the physicians in those cities, I was given the opportunity to examine patients, to see autopsy material, and to go over hospital and statistical records in order to accumulate some idea of the frequency of the different kinds of heart disease and of cardiovascular disease as a whole in much of Africa. I did not visit the northwestern part of the continent, but I have been told that somewhat the same situation exists in the southern part as we found in the republics of the Congo and Gabon. In the northernmost part of West Africa there is apparently some similarity with the findings in Egypt.

Let me take up the various kinds of heart disease as I saw them or as I was told about them on this African visit.

Congenital heart disease I found everywhere, quite possibly in the same relative degree as we see it ourselves, although, as a rule, there are only crude statistics available. Patency of the ductus arteriosus, septal defects, and the tetralogy of Fallot are not at all rare, and here and there, surgical correction of these lesions is being carried out, especially in South Africa.

Rheumatic heart disease is common in all the countries I visited, and ranks about even with hypertensive heart disease in Egypt and in South Africa. It is somewhat less common than hypertensive heart disease in Equatorial Africa. Rheumatic fever, as such, is often difficult to recognize, but the valvular lesions which result from it are quite common, and a number of lesions are being corrected surgically, especially, of course, mitral stenosis.

Syphilitic cardiovascular disease is becoming rare throughout Africa, although in some less advanced areas, several per cent of the cardiovascular cases are still due to syphilis.

Infestation by Schistosoma (the Bilharzia parasite) is quite common in certain areas, especially Egypt and East Africa. It is responsible in some places for a third of all the cases of hypertension and at least a few of the cases of chronic cor pulmonale.

Cor pulmonale due to pulmonary disease and obstruction of the pulmonary circulation is quite frequent in many of the countries. Apparently, it is due largely to fibrotic changes in the lungs secondary to infection or to emphysema, but also, although much less commonly, to actual blocking of the pulmonary circulation by the Bilharzia ova.

One of the most interesting of my medical experiences was the finding of two other types of heart disease which are rare in the Western world. The most extraordinary is that which has been called by Davies, of the Makerere Medical School in Kampala, Uganda, *endomyocardial fibrosis* (with or without elastosis, which as such is a different entity). Although it is rarely seen elsewhere in Africa, this condition of extensive deformity of the heart muscle, in particular by fibrosis and calcification, is quite common in East Africa among the Blacks. It ranks there about even in prevalence with rheumatic heart disease, and, on occasion, resembles it clinically, often occurring as it does in relatively young adults. Dr. Davies showed me many examples in his collection of pathologic specimens, and I saw a few clinical cases. The cause of this fantastic disease is unknown. It has been variously attributed to infection, to malnutrition, and to other factors ill defined.

A second type of unusual heart disease that I encountered occasionally in all parts of Africa is probably somewhat like that which we see elsewhere in the world, namely, *cardiac enlargement and failure*, mostly left ventricular, *of unknown cause*, which occurs at all ages. I saw a number of such specimens and cases, especially in South Africa.

Pericarditis is common in Africa, including that

associated with rheumatic heart disease and myocardial infarction. The usual infectious factors are to blame, particularly viral and tuberculous factors. As a result of the more effective treatment of tuberculosis by antibiotics in the last few years, more cases of constrictive pericarditis have been seen recently in Egypt, and now are being more actively treated by pericardial resection. When tuberculosis as an infection decreases, there will be less of this type of operation to perform.

Hypertensive heart disease is common everywhere, and is actually, I believe, the most common of all types of heart disease throughout the continent. Why hypertension is so common is not at all clear, but it is apparently found even in the remote parts of the jungle, although much more investigation as to this matter needs to be made. This subject is of considerable interest because we have long wondered whether hypertension in the American Negro has been acquired since his arrival in the Western world. Hypertension accounts for as much as 50 per cent or even more of all cardiovascular cases in tropical West Africa. Cerebrovascular involvement does occur, but much less commonly than the cardiac sequelae.

Finally, *coronary heart disease* varies extraordinarily in its prevalence in Africa. It is quite common in Egypt, especially among the well-to-do, and also in East and South Africa among the Whites and East Indian populations, but it is very rare, at least in youth and middle-aged persons, among the Blacks, especially the Bantus. In the Bantus, atherosclerosis of the coronary arteries of moderate degree is found in the oldest age group, but it rarely leads to involvement of the heart, and then only at a very different age than in the Whites and East Indians. This situation is somewhat like that found in Southern Japan, where the disease is most prevalent among the older age group, and in this respect there is a difference of about 25 years of age between the Southern Japanese on Kyushu at Fukuoka and the Bostonians in the U.S.A. represented at autopsy at the Massachusetts General Hospital. A comparison of the degree of coronary atherosclerosis in 350 Japanese adults with that seen in a similar number of adults at the Massachusetts General Hospital showed the same levels in the Boston population at the age of 45 years as in the Fukuoka population at the age of 70 years. The reason for this great discrepancy in the degree of coronary atherosclerosis and its effect on the heart through the complication of thrombosis is one of the prime reasons for the need to intensify international epidemiological cardiovascular research. Whether race plays a role or, more likely, whether the ways of life are the cause, we do not know yet for certain, but it is true that the Bantu is just beginning to emerge from his primitive ways of life, under the influence of which in the past he has been much undernourished and yet usually more active physically than his white neighbor. The mixed Colored population of Cape Town holds an intermediate position, as to the prevalence of coronary heart disease, between the extremes found among the Whites, on the one hand, and the Bantus, on the other.

Arrhythmias, neurocirculatory asthenia, and cardiac neurosis seem to be universal throughout Africa, as in other parts of the world.

In conclusion, I believe that much profitable cardiovascular epidemiological research can be done in Africa to increase our knowledge of the factors responsible for heart disease, and that such research can eventually lead to protection of people throughout the world from the heart diseases still found in youth and middle age.

*Paul D. White, M.D.**
Boston, Mass.

*The author will be glad to refer the reader to tables of the racial incidence of different types of cardiovascular disease in Egypt, East Africa (Kenya and Uganda), Cape Town (South Africa), and Leopoldville (the Belgian Congo).

Right ventricular hypertension as a cause of precordial pain

Chest pain like that of angina pectoris due to coronary atherosclerosis is frequently encountered in young individuals who suffer from a variety of circulatory abnormalities associated with high right ventricular pressure. We have recently observed such a patient, a 19-year-old farm boy with exertional chest pain in whom a positive electrocardiographic exercise test showed a 2-mm. depression of the S-T segments after standard exercise. In this patient with a "typical ischemic" response to exercise, pulmonary hypertension was associated with a large patent ductus arteriosus. The patient died during operation, and at autopsy the coronary arteries were found to be normal. The myocardial ischemia responsible for the anginal pain was presumed to be the result of altered hemodynamics. Similar pain in the presence of normal coronary arteries has been reported in patients with pulmonary stenosis. The finding of fibrosis of the right ventricle in patients with this disease supports the conclusion that the pain originates in an ischemic right ventricle.[1]

The right ventricular systolic pressure is normally less than the diastolic pressure in the aorta, and hence right ventricular coronary flow continues throughout systole, whereas left ventricular coro-

nary flow ceases.[2] The systolic right ventricular intracavitary pressure is, therefore, an important determinant of right ventricular coronary flow, and ischemia might be anticipated in association with elevated right ventricular pressure. Right ventricular hypertension cannot be the only factor involved, since right ventricular pressures of the same or greater magnitude are found in the presence of ventricular septal defects in association with either pulmonary stenosis or pulmonary vascular disease, yet angina pectoris does not occur.[3]

In the presence of an intact intraventricular septum, right ventricular pressure may exceed left ventricular pressure, especially in patients with pulmonary stenosis. When the septum is intact, the diastolic pressure in the hypertensive right ventricle may be elevated and exceed the diastolic pressure in the left ventricle. With a large ventricular septal defect, pressures in the two ventricles remain equal throughout the cardiac cycle. It may be that the effect of these diastolic pressure relationships on the collateral circulation in the heart explains the presence of angina pectoris only in patients with right ventricular hypertension and an intact septum.

The fact that angina pectoris is not universally present in association with right ventricular hypertension seems best explained by the normal variability in the anatomy of the coronary circulation. The available clinical observations indicate that the chest pain of patients with pulmonary stenosis and pulmonary hypertension is the result of right ventricular myocardial ischemia secondary to reduced coronary flow. It seems reasonable to explain the reduced coronary flow on the basis of the elevated right ventricular intracavitary pressure during both systole and diastole.

Richard S. Ross, M.D.
Baltimore, Md.

REFERENCES

1. Lasser, R. P., and Genkins, G.: Chest pain in patients with isolated pulmonic stenosis, Circulation **15**:258, 1957.
2. Gregg, D. E.: Coronary circulation in health and disease, Philadelphia, 1950, Lea & Febiger.
3. Stuckey, D.: Cardiac pain in association with mitral stenosis and congenital heart disease, Brit. Heart J. **17**:397, 1955.

Control of body fluid volume

The volume of fluid in the body is controlled within narrow limits, for 70 per cent of the adult body is fluid, and when measured under standardized conditions, total body weight varies less than ± 1 per cent over long periods, as Fowler[1] has shown. Although the stability of this volume in normal people has been recognized since the work of Henderson,[2] the mechanism by which this regulation is accomplished has not been adequately explained.

Variations in temperature, growth, and control of osmotic pressure of the body fluids influence the water content of the body. If, after the effects of these systems have been accounted for, independent control of the volume of body water occurs, then one must postulate that volume control per se exists. Since Peters[3] first discussed the concept of a "volume receptor," many workers have examined this problem. Borst[4] postulated that the vascular compartment monitored changes in fluid volume to alter cardiac filling pressure and output; changes in cardiac output cause variation in the amount of sodium and water retained. Lowe and Sayers[5] made clinical observations on edematous patients and concluded that a volume-controlling mechanism existed with volume-disturbing and volume-restoring components, and that the sensitivity of this mechanism was altered in edematous states. Recently, Lowe[6] has presented data collected from normal individuals and those with a disturbance in their regulation of fluid storage. From these observations a hypothesis was elaborated. The body is regarded as a storage of a complex fluid in many compartments. Through the vascular compartment a continuous inflow and outflow of solvent and solute occurs. The fluid in this compartment is monitored for osmotic pressure and changes in volume, and from this information the inflow and outflow of solvent is adjusted by means of a feed-back control, thus achieving self-regulation of the volume of the system. This view is challenging but reasonable and there is other evidence to support it.

The osmotic pressure of the vascular compartment is controlled by the intake and excretion of water and salt. Verney[7] has shown that osmoreceptors in the hypothalamus respond to changes in tonicity of the extracellular fluid and so regulate the secretion of antidiuretic hormone by the neurohypophysis; the antidiuretic hormone ensures adequate retention of water by the renal tubules. With this mechanism functioning, the volume of extracellular fluid will depend on the amount of sodium present. This is normally controlled by the salt-retaining hormone, aldosterone, which is secreted by the zona glomerulosa of the adrenal cortex and also acts upon the renal tubules.

Experiments designed to show the relation between the sodium in the vascular compartment and the secretion of aldosterone support the interpretation that this is brought about by the effect of sodium on extracellular fluid volume. Bartter, Mills, Biglieri and Delea[8] compared changes in extracellular fluid volume produced by infused water, isotonic saline, and hypertonic saline loads with that produced by albumin, phlebotomy, and red cell reinfusion. It appeared that extracellular fluid volume exercised a control over the secretion of aldosterone. Occlusion

of the inferior vena cava above the liver increased the secretion of aldosterone. This increase was maintained, after release of the constriction, if the vagi in the neck were divided during the experiments but not with the vagi intact. Vagal section alone did not alter the secretion of aldosterone. Similarly, it was found that constriction of the common carotid artery low in the neck produced increased secretion of aldosterone, but that this did not occur if the carotid sinus was denervated beforehand. McCally, Anderson and Farrell[9] placed sutures through the atria of dogs. Whereas traction on the right atrium depressed the secretion of aldosterone within an hour, stretching the left atrium was without effect. The afferent limb to release of aldosterone, therefore, appears to depend on an unusual physiologic mechanism, in that the stimulus of decreased baroceptor stimulation leads to increased production of aldosterone, but removal of the stimulus alone will not reduce secretion. For this a second mechanism involving the vagus nerve is required. The evidence so far suggests that the receptors lie in the right auricle or great veins, although receptors at other sites may play some part. Pearce[10] found that vagotomy and denervation of the carotid sinus did not prevent the diuresis which followed expansion of the plasma volume with isotonic infusion. He concluded that additional receptors must contribute to the afferent component.

Observations on dogs by Rauschkolb[11] and Farrell[12] suggested that the secretion of aldosterone was stimulated by a hormone from the brain. Recent work by Davis[13] and Denton, Goding and Wright[14] has strengthened this view. Davis showed, by cross-circulation experiments, that if the blood from a dog with inferior vena caval obstruction was passed through the adrenals of a normal dog, the secretion of aldosterone increased, and fell again when the cross-circulation was stopped. Denton, Goding and Wright used trained conscious sheep with neck adrenal transplants for adrenal infusion and arterial cross-circulation experiments, measuring changes in salivary electrolytes, but not aldosterone itself. They found that changes in the concentration of electrolytes in the blood of the adrenals may be a contributory cause of changes in electrolyte-active steroid secretions occurring in sodium-deficiency but could not account for the whole range of function recorded. The cross-circulation experiments showed that there was a considerable stimulus to secretion from the adrenals of electrolyte-active steroid when the blood of a sodium-depleted, adrenally insufficient donor animal was passed through the adrenal transplant of another animal which was in normal sodium balance. Since this stimulation did not appear to be due to corticotrophin, action by a tropic hormone appears probable. The central integration of information received from the afferent loop and the site of tropic hormone formation is unknown. Farrell[15] has recently reported that this hormone is concentrated in the region of the pineal and subcommissural body.

The raised levels of aldosterone in patients with edema and ascites make it clear that control does not depend upon total extravascular fluid volume. In these cases it can be argued, as Ross[16] has suggested, that there is an increase in extracellular volume, but not an increase in the area of the vascular compartment which monitors volume. Any disturbance, then, of Starling's[17] equilibrium will permit an excessive flow of water and solutes through the capillary wall, resulting in reduction of the vascular volume and stimulation of the aldosterone-secreting mechanism. If this capillary leak persists, hyperaldosteronism will continue to result in further retention of sodium and accumulation of fluid. In congestive cardiac failure, nephrosis, and the edema of hypoproteinemia the disturbance is general, and generalized edema will result when the lymphatic pathways are unable to drain the excess fluid. If the disturbance is localized, as in the case of elevated intrahepatic portal pressure, sequestration of fluid into the peritoneal cavity will occur. Courtice and Simmonds[18] have shown that this fluid is drained principally by the lymphatics of the diaphragm into large collecting ducts in the thorax. As this system becomes fully loaded (and its carrying capacity is large), ascitic fluid collects, reducing the effective plasma volume and setting in motion the process which leads to the retention of salt and fluid.

Although many gaps remain in our knowledge of the control of body fluid volume, the pattern of the regulating mechanism is emerging. Receptors monitor the volume of some portion of the vascular compartment and so activate a neuronal-endocrine feed-back pathway which acts on peripheral targets to produce the changes essential for keeping body fluid volume within narrow limits.

R. G. Wyllie M.B., B.S.
Melbourne, Australia

REFERENCES

1. Fowler, R., Jr.: Control of body water content: a study of day-to-day variation, in humans and rabbits, Australasian Ann. Med. **4**:123, 1955.
2. Henderson, L. J.: On volume in biology, Proc. National Acad. Sc. **2**:654, 1916.
3. Peters, J. P.: Body water, Springfield, Ill., 1935, Charles C Thomas.
4. Borst, J. G. G.: The maintenance of an adequate cardiac output by the regulation of the urinary excretion of water and sodium chloride; an essential factor in the genesis of edema, Acta med. scandinav. **130** (Suppl. 207), 1948.
5. Lowe, T. E., and Sayers, B. M. A.: Control of the water content of the body, Australasian Ann. Med. **1**:51, 1952.
6. Lowe, T. E.: The nature of the control of body fluid volume in man, Phys. Med. Biol. **4**:126, 1959.
7. Verney, E. B.: The antidiuretic hormone and the factors which determine its release (Croonian Lectures), Proc. Roy. Soc., London, B **135**:25, 1947.
8. Bartter, F. C., Mills, I. H., Biglieri, E. G., and Delea, C.: Control and physiologic action of aldosterone. *In* Recent progress in hormone research, New York, 1959, Academic Press, p. 311.
9. McCally, M., Anderson, C. H., and Farrell, G. L.: The effects of atrial stretch on aldosterone secretion, Proceedings of the 40th Meeting,

Endocrine Society, San Francisco, 1958, p. 119.
10. Pearce, J. W.: The effect of vagotomy and denaturation of the carotid sinus on disuresis following plasma volume expansion, Canad. J. Biochem. & Physiol. **37**:81, 1959.
11. Rauschkolb, E. W., and Farrell, G. L.: Decreased aldosterone secretion in decapitated dogs, J. Clin. Endocrinol. **16**:915, 1956.
12. Farrell, G. L.: Abstracts of meeting of endocrine society, New York, 1957, p. 32.
13. Davis, J. O.: Proceedings of the Laurentian Hormone Conference, 1958. *In* Recent progress in hormone research, New York, 1959, Academic Press, p. 298.
14. Denton, D. A., Goding, J. R., and Wright, R. O.: Control of adrenal secretion of electrolyte-active steroids, Brit. M. J. **2**:447 and 522, 1959.
15. Farrell, G. L.: The physiological factors which influence the secretion of aldosterone. *In* Recent progress in hormone research, New York, 1959, Academic Press, p. 275.
16. Ross, E. J.: Aldosterone in clinical and experimental medicine, Oxford, 1959, Blackwell Ltd., p. 107.
17. Starling, E. H.: On the absorption of fluids from the connective tissue spaces, J. Physiol. **19**:312, 1896.
18. Courtice, F. C., and Simmonds, W. J.: Physiological significance of lymph drainage of the venous cavities and lungs, Physiol. Rev. **34**:419, 1954.

Ultrastructure of coronary vessels

The student of coronary heart disease, should he not be personally conversant with a variety of techniques and disciplines, depends on information obtained by the clinician, statistician, biochemist, physiologist, morbid anatomist, and histologist. The field is widening and the electron microscope is now becoming significant.

The information on detailed structure that has become available in the last few years, in a variety of tissues, has not only been astonishing (both confirming and extending observations made at the upper limits of resolution of the light microscope) but promises a thoroughly satisfactory integration of structural and functional findings. Every tissue has been illuminated and its intimate secrets revealed—even if many are still not understood.

New techniques require different yardsticks. Here tissue fixation must be immediate—the slight delays that were apparently unimportant in ordinary histology allow serious demonstrable changes in fine cytological structure. Hence, at present, attention must usually be directed to experimental material to the exclusion of human tissues. Within this range, important information is obtainable. In addition to observations on muscle, others have been made on the ultrastructure of the various layers of blood vessels, from the aorta to the capillaries. In different vessels, endothelium,[1-3,5-7] elastic tissue,[7] and smooth muscle[5,7] have all been studied.

In the coronary vessels the endothelial lining is a continuous sheet, the cells overlapping at their margins.[5,7] Some of these send processes through the internal elastic lamina, which is thus a fenestrated sheet[7]; these may be important in the transfer of material to deeper layers. The phenomenon of uptake of material by cells—the pinocytosis described by Lewis,[4] in 1931—has now been observed at a new level.[5] Other cytological details have been noted but their significance is still speculative.

Atherosclerosis induced by the feeding of cholesterol has been studied in the aorta[1] and coronary arteries.[8] Globules of material, presumably lipid, were apparent overlying endothelial cells in the stage of acute lipemia; some of these were porous, enclosing irregularly shaped vacuoles.[8] This material appeared to be also within and beneath the endothelial cells.

The internal elastic lamina showed irregular focal swelling, with corresponding loss of density and of fine fibrillar structure. This was deduced to be due to solid solution of lipid in the elastic tissue. Changes in smooth muscle, such as formation of cytoplasmic vacuoles, and increase in intercellular collagenous material were also demonstrated. Such appearances in presumable muscle cells may support some of the earlier views regarding the origins of foam cells. Despite the conjectural nature of some of the suggestions the observations are clear-cut. Human atherosclerosis may be (and in some forms undoubtedly is) different from the experimental condition described, in which the principal process is transfer of fat from the lumen to the blood vessel wall (especially the elastic tissue), but this type of study does provide basic information of undoubted significance for the elucidation of lipid interchange and deposition in vessel walls.

Electron microscopy is still in the earliest stages of development. Its present rate of growth suggests an embryonic rather than even an infantile phase of evolution, but its potential importance cannot be overemphasized. The purpose of this note is to draw attention to this newcomer to the family of technical auxiliaries in the study of the structure of coronary vessels and of coronary disease.

E. S. J. King, M.D., M.S., D.Sc.
Melbourne, Australia

REFERENCES

1. Buck, R. C.: Fine structure of aortic endothelial lesions in experimental cholesterol atherosclerosis of rabbits, Am. J. Path. **34**:897, 1958.

2. Fawcett, D. W., and Selby, C. C.: Observations on the fine structure of the turtle atrium, J. Biophys. & Biochem. Cytol. **4**:63, 1958.
3. Karrer, H. E.: The ultrastructure of mouse lung, J. Biophys. & Biochem. Cytol. **2**:241, 1956.
4. Lewis, W. H.: Pinocytosis, Bull. Johns Hopkins Hosp. **49**:17, 1931.
5. Moore, D. H., and Ruska, H.: The fine structure of capillaries and small arteries, J. Biophys. & Biochem. Cytol. **3**:457, 1957.
6. Palade, G. E.: Fine structure of blood capillaries, Appl. Physics **24**:1424, 1953.
7. Parker, F.: An electron microscope study of coronary arteries, Am. J. Anat. **103**:247, 1958.
8. Parker, F.: An electron microscopic study of experimental atherosclerosis, Am. J. Path. **35**:19, 1960.

Letter to the Editor

Digital computer analysis of the electrocardiogram

Institute of Physical Medicine
and Rehabilitation
400 East 34th Street
New York 16, N.Y.
September 12, 1960

To the Editor:

This communication is to announce the availability of a general purpose computer program for a machine abstraction for electrocardiographic wave amplitudes, durations, and areas from scalar leads. The program was written for an IBM 650 digital computer. Input voltage data must be in digital form taken at equal time intervals of 5 milliseconds or more. Up to three scalar leads can be processed simultaneously.

Output data presents: (1) the equation for the reference "isoelectric line"; (2) the timing of each wave, beginning, ending, and maximal amplitude for all positive and negative waves about an arbitrary magnitude to be set by the investigator; (3) the maximal wave amplitude, relative wave areas, and ST-segment displacement information and timing.

A more detailed 15-page operating manual will be provided upon request.

This author received encouragement and support from the Heart Control Program and from the National Heart Institute, United States Public Health Service.

Lee D. Cady, Jr., M.D., Dr. P.H.

Book reviews

Electron Microscopy of the Cardiovascular System. An Electron Microscopic Study With Applications to Physiology. By Bruno Kisch, M.D., Professor and Medical Director, Yeshiva University; Director, Electron Microscopic Research Institute, Elmhurst City Hospital at New York; Professor Emeritus, University of Cologne, Cologne, Germany. Translated from the original German text by Arnold I. Kisch, M.D., New Haven, Conn. Springfield, Ill., 1960, Charles C Thomas, 180 pages. Price $7.50.

The title of this book is somewhat misleading, because from it one expects a description, at the electron microscopic level, of the entire cardiovascular system. Actually, no part of the cardiovascular system, except the heart, is even touched upon.

A large part of the book is devoted to the ultrastructure of muscle, both skeletal and cardiac. An attempt is made to review some of the earlier work on muscle, but the author gives insufficient recognition to the real pioneers in the electron microscopic study of muscle. In his discussion of muscle fiber, the author dwells at length on myofibrils, sarcosomes (mitochondria), striations, and nuclei; however, he barely touches on the endoplasmic reticulum, which is an important component of muscle as well as of other types of cells, and which has been studied extensively with the electron microscope.

This book is actually a review of the author's own work of the last ten years, to which he adds his own (sometimes questionable) interpretations of the work of others. Nomenclature is inconsistent and the wording is poor, so that it is often difficult to understand the author's meaning.

Apparently, the many electron photomicrographs used in the book were all from the author's laboratory. The quality of the micrographs ranges from good to poor.

Electrophysiology of the Heart. By Brian F. Hoffman, M.D., Associate Professor of Physiology, College of Medicine, State University of New York, Downstate Medical Center, Brooklyn, N.Y.; and Paul F. Cranefield, Ph.D., Associate Professor of Physiology, College of Medicine, State University of New York, Downstate Medical Center, Brooklyn, N. Y. New York, 1960 McGraw-Hill Book Company, Inc., 323 pages. Price $12.50.

This book is a summary of available information about the transmembrane potentials of single cardiac fibers as registered by microelectrode techniques, much of it previously unpublished. After introducing the methods and the Hodgkin ionic theory of the action potential, the authors have systematically described the characteristics of the action potentials found in the major types of cardiac fibers (atrial, ventricular, sinoatrial nodal, atrioventricular nodal, and Purkinje) and the effects of physiologic variables upon each.

The text is lucid and the presentation logical and straightforward. A wide audience has been kept in mind by the sound early introduction of preparatory definitions. However, one exceptional obstacle to clarity for the general reader in the field of cardiology was noted: the term *regenerative depolarization* was frequently encountered and never adequately defined. Careful comparison of contexts allowed the inference that both local and propagated responses were included, and that *regenerative* was used in the sense of *autoaccelerative*, but the electronic basis for such usage was not made clear.

The reviewer strongly recommends this book to the serious student of the electrical behavior of cardiac muscle, whether he be biophysicist, physiologist, or physician.

Edema. Mechanisms and Management. Edited by John H. Moyer, M.D., Professor and Chairman, Department of Medicine, Hahnemann Medical College and Hospital; and Morton Fuchs, M.D., Assistant Professor of Medicine, Hahnemann Medical College and Hospital, Philadelphia, Pa. Philadephia, 1960, W. B. Saunders Company, 833 pages. Price $15.00.

Many individuals contributed papers on various aspects of the problems relative to edema which formed the program of the Symposium on Edema, Mechanisms and Management. The papers are included in this monograph. Some of the discussions are interesting and thought-provoking, whereas others are dull or simply restate concepts of many years' duration, without indicating the discrepancies between theory and fact. For example, on pages 4 and 5 the statement is made that the transcapillary hydrostatic pressure which tends to promote a loss of water from the tissue is equal to the oncotic pressure which tends to return the fluid. The author then states that those who came to the Symposium on a bus had their legs down for a long time. After introducing this concept, he fails to indicate why all of them did not have their legs greatly distended with edema fluid, knowing how rapidly fluid and electrolytes traverse the capillary walls. Nor does he point out why it is, if transcapillary hydrostatic and oncotic forces are equal, and transcapillary fluid exchange is simply regulated by such forces, that all people are without gross evidence of edema of the legs all day, why tall people do not normally have much more edema of the ankles and feet than short ones, or why patients have high venous pressure without clinical evidence of edema. If a symposium is to settle

questions, the fundamental problems should be constantly before the participants and clearly defined. Conventionally accepted concepts and theories which fail to explain established observations should be presented with apologies and warning, or be presented to show their inadequacies. Old errors and discrepancies should not be repeated constantly without regard for the need to elucidate them.

The chapter on the lymphatic system and its influence on extracellular fluid balance is no more mature or thought-provoking than a brief comment made to freshman medical students or to premedical students in a class of zoology. The mature members of the audience must have been extremely bored, in view of the many important questions that could have been asked and answers that could have been discussed. Furthermore, little effort was made throughout the monograph to indicate what the original observations were and who made them. This Symposium also reflects another trend in American medicine to abandon well-tested therapeutic procedures for new ones which have not been adequately evaluated. For example, the papers on the treatment of the edema of congestive heart failure de-emphasize the use of mercurial diuretics which are still excellent and are usually more effective than the new ones, such as the chlorothiazide type of preparations which have important subtle harmful effects which are sometimes fatal. This approach is due in part to the fact that some who wrote on the management of the disease states are not experienced clinicians and cardiologists who have daily responsibilities to patients, but are primarily laboratory investigators.

Some papers are brief and the statements made are not documented with research data. This is particularly true of the article on forward and backward failure on page 704, which is more a philosophical approach than a discussion of research. The monograph consists of too many short notes on too many subjects; few important problems were thoroughly or profoundly discussed.

A number of the discussions were highly opinionated. At times the moderator had to ask questions to keep the discussions in progress. A number of the participants who were discussing complex problems in the formation of edema had not performed research for many years and had not been actively engaged in the study of the fundamental aspects of the formation of edema. This was reflected by the superficial nature of the presentations, questions, and discussions.

The sections on the kidney were better presented, but they really added little that is new and failed to provoke any profound discussion.

Medical students who might profit most from this book will find it impossible to orient the research and investigators in time and contribution. In many instances, experiments performed years before were merely repeated by modern methods and apparatus with far less imagination and thought.

The purpose of the Symposium may have been achieved. It would seem, however, that most symposia today devote most of their time to rehashing ideas already well known to the participants instead of embarking immediately on a few provocative presentations with much discussion to consider thoroughly only a few problems rather than the entire field. Anyone invited to attend such a symposium should be expected to know the usual concepts or he would not qualify for invitation. Perhaps we need fewer but more mature symposia. This book makes available to researchers of the world the discussions presented at a representative type of midtwentieth century symposium on a special subject in clinical medicine.

If the reader wishes a conventional summary of "tidbits" on edema, he will find the book useful. A medical student or anyone beginning a study of the formation and management of edema will find this book to be a start in his reading. If he is engaged in research in the field, he will find it necessary to read a great deal before he discovers an interesting or new point.

Grundriss und Atlas der Elektrokardiographie. By Rudolf Zuckermann, Dr. med. habil.; Facharzt für Kardiologie; Oberarzt an der Kinderklinik der Martin-Luther-Universität Halle-Wittenberg und Leiter der kardiologischen Abteilung; Professor mit Lehrauftrag für Kardiologie. Third edition, Leipzig, 1960, Georg Thieme, 620 illustrations, 660 pages. Price: geb. DM 72,15.

This book was first published in 1955, under the title *Atlas der Elektrokardiographie.* Since then it has been expanded as the *Grundriss und Atlas der Elektrokardiographie,* and now covers about 650 pages. As mentioned in the foreword of the first edition, it is based on the personal experience gained by the author at the Institute of Cardiology in Mexico.

Electrocardiographic theory is summarized and takes up only 18 pages. This is followed by a rather large section which covers the different lead systems. A section on vectorcardiography describes the principle, the main lead systems, and some schematic vectorcardiograms of normal subjects, of patients with right and left hypertrophy, as well as of patients with right and left bundle branch block. Then the normal ECG, its variations, and its measurements are described. Also, the pathologic ECG is summarized, with several instructive schemata. The atlas contains several examples of electrocardiograms which are analyzed specifically and discussed extensively, including the different forms of arrhythmias. Finally, a summary of the electrocardiograms of different animals is mentioned.

This book cannot be judged as a textbook, since the theoretical part presupposes the readers' knowledge of the main principles, which are not extensively discussed. But the cardiologist will

find many interesting facts. The author's tendency to use a special terminology makes the understanding rather difficult for non-German readers. He mentions, for instance, a normal-P, P-mitrale, P-pulmonale, P-congenitale, bilateral enlargement of the atrium, P-infantile, tension-P, hypertonic ST-depression, and a so-called blocking QRS-complex in Lead V_1.

ELECTROCARDIOGRAPHIC TECHNIQUES. A MANUAL FOR PHYSICIANS, NURSES, AND TECHNICIANS. By Kurt Schnitzer. Second edition, New York, 1960, Grune & Stratton, Inc., 109 pages. Price $4.75.

The value of any book is determined by its usefulness to its readers. It is impossible to know the appeal of a book on this subject. The intended readers are quite heterogeneous, for physicians, nurses, and technicians differ widely in knowledge, clinical responsibility, and experience. However, the book must have proved useful, since it is now in a second edition.

The manual includes a brief discussion of cardiac terminology, the electrocardiogram, the electrocardiograph, the technique of recording and mounting tracings, and other obvious considerations of a subject of this nature.

Certain points are worth noting. For example, no mention of the qualifications and interest of the author is given on the title page. Readers would like to know whether he is on the faculty of a medical school or the staff of a hospital, and his title or rank. The author fails to distinguish between his own ideas and the procedures of general practice and recommendations of procedure by responsible cardiologists and institutions: e.g., the code used for marking each lead. He fails to emphasize the need for care of the instruments, the electrodes, the heart station, the records, and other facilities which insure work of the highest quality. The quality of electrocardiographic recordings depends upon good guidance, experience, and the high demands of the doctor and institution. Most of the references in the bibliography are too technical, specialized, or controversial for nurses, technicians, and general physicians. More useful references have been omitted.

Vectorcardiography is not adequately presented. The technique depends so much on the apparatus, reference frame employed, and objectives of the investigator that the subject should have been omitted until vectorcardiography is standardized for general clinical use.

This manual can be of some value, but it cannot replace careful training in the heart station, clinic, laboratory, and at the bedside. Nor can it replace the constant demands for high quality by a doctor who knows high-quality electrocardiography.

THE CLINICAL USE OF ALDOSTERONE ANTAGONISTS. Compiled and edited by Frederic C. Bartter, M.D., Chief, Section of Clinical Endocrinology, National Heart Institute, National Institutes of Health, Bethesda, Md. Springfield, Ill., 1960 Charles C Thomas, 211 pages. Price $5.00.

This book records the proceedings of a conference sponsored by G. D. Searle & Co., in Chicago, Ill., Oct. 16, 1958, in which 23 investigators summarize a limited experience with the 17-spirolactone steroids. These drugs, of which spironolactone (Aldactone, Searle) is the most potent, have been shown to antagonize the action of aldosterone on electrolyte excretion, and, as such, they represent an interesting new class of diuretic agents aimed at reversing the contribution of hyperaldosteronism in sodium-retaining disorders. Their greatest effectiveness as natriuretic agents is in cirrhosis with ascites and the nephrotic syndrome, conditions in which hyperaldosteronism has been shown to play an important role in the development and maintenance of edema. The results in congestive heart failure are more tenuous, although worthy of further study, particularly since these drugs are most effective as potentiators of the action of other diuretics, including the thiazides and mercurials. Extensive clinical trials have been impeded by the scarcity of the compounds and the relatively high cost of the drugs. A clinically useful property of these drugs is that, in contrast with other diuretic agents, undesirable loss of potassium does not accompany the natriuresis, and actual retention of potassium may be observed.

The book is recommended for practitioners who treat patients with refractory edema of various etiologies, and for those students and physicians interested in current research in sodium and water metabolism.

ATRIAL SEPTAL DEFECT. By H. Gosta Davidsen. Copenhagen, 1960, Ejnar Munksgaard, 225 pages. Price: D. kroner 50.

The study of congenital heart disease has progressed so much in the last decade that few will be surprised to find a sizable monograph devoted solely to the subject of atrial septal defect. In this work the pertinent literature up to 1959 has been carefully reviewed and integrated with an account of 132 cases studied personally by the author. The subject is covered exhaustively, including a careful account of the embryologic development of the atrial septum, and a tabular summary of 190 autopsied cases gathered from the literature. The cases of the author were studied in Rigshospitalet, the University Hospital of Copenhagen. Twenty per cent of the

patients were found to have "tight mitral stenosis." This group included patients in whom the mitral orifice was too small to admit two fingers, and those with retraction of the valve or thickening and shortening of the "subvalvar apparatus." Such lesions were not associated with a clinical history of rheumatic fever, and were much more frequent in patients over 30 years of age. The atrial septal defects were usually in the central portion of the auricular septum. Secondary development of the septal defect could not be substantiated. Differences in mean atrial pressure are believed by the author to play a central role in determining the degree and direction of shunting, but confirmatory evidence is lacking—possibly because of technical difficulties in measuring atrial pressure gradients.

The English style is clear and readable. The printing and format are excellent, but the use of a flimsy paper cover is regrettable. This monograph provides a thorough and critical review of current knowledge of the anatomy, altered physiology, and clinical manifestations of a common cardiovascular defect. It should be in the permanent library of every serious student of congenital heart disease.

Cardiac Emergencies and Related Disorders. Their Mechanism, Recognition and Management. By Harold D. Levine, M.D., Senior Associate in Medicine, Peter Bent Brigham Hospital, Boston, Mass., and Assistant Clinical Professor of Medicine, Harvard Medical School. Clinton, Mass., 1960, The Colonial Press, Inc., 381 pages, 44 illustrations. Price $12.

This monograph is devoted to the recognition and treatment of acute cardiac emergencies. It includes chapters on acute left ventricular failure, cardiogenic shock, cardiogenic chest pain, episodes of tachycardia and arrhythmia, as well as Adams-Stokes disease, syncope, cardiac arrest and resuscitation. The primary emphasis is on the clinical approach to recognition of these problems and on practical measures of treatment. The author evidently has drawn extensively both upon his own clinical experience and that of his associates.

A bibliography is included which, while not encyclopedic, will be helpful to the reader. Numerous helpful points, both clinical and electrocardiographic, are made in the diagnosis of cardiac arrhythmias and tachycardias.

In some instances, the author has apparently taken some liberties in expressing his opinion about matters which may be controversial. Thus, in regard to the use of vasopressor substances in cardiogenic shock is his statement that "Withal it must be conceded that there is no overwhelming statistical evidence for the value of these drugs. Only an occasional patient is salvaged." Such a statement cannot be considered representative of an extensive sampling of the results reported in the recent literature. Likewise, in the section concerning acute myocardial infarction, he states, "The common practice of routine hourly or two-hourly blood pressure determinations around the clock is superfluous and deprives the patient of badly needed rest." This is debatable, in the opinion of the reviewer. If anything, more careful monitoring of blood pressure levels and arrhythmias, even by electronic and mechanical means, is needed in order to detect the early appearance of these complications in this disease. Such careful observation, with early recognition of these aberrations, may indeed be lifesaving.

There are also many experienced clinicians who will probably take issue with the view that, "Starting as early as the first or second day, as long as he is not in shock, the patient with acute myocardial infarction should be out of bed, seated in a well-padded chair for as many hours of the day as he will tolerate." This "armchair" treatment has been the basis for much stimulating discussion. Although some studies suggest that this treatment is beneficial, final evidence that it improves the morbidity and reduces the mortality is, as yet, however, wanting. The author would have done better to indicate that this latter therapy is still somewhat *sub judice*.

The volume is well written, replete with good clinical experience, and will be valuable to students, house officers, and practitioners generally. It should be helpful to anyone who has to deal with acute cardiac emergencies.

Announcements

Awards totaling $30,000 for medical work in arthritis and heart disease were announced today by J. A. Gairdner, Toronto industrialist and financier and President of the Gairdner Foundation, Toronto, Canada.

Four American and two British medical scientists share the awards, and each will receive a prize of $5,000. The winners are:

Dr. John H. Gibbon, Jr., Professor of Surgery and Director of Surgical Research, Jefferson Medical College, Philadelphia, in recognition of Dr. Gibbon as the first man to develop and successfully use an artificial heart for the surgical correction of a heart defect in human beings.

Dr. William F. Hamilton, Professor of Physiology, University of Georgia School of Medicine, for his work in the use of dyes injected into the blood stream to determine blood flow and distribution in the treatment of heart disease.

Dr. Karl Meyer, Dean of Medicine, Columbia University, New York, for his contributions to the modern concepts of the chemical structure and functions of the so-called binding substances of connective tissues, main supporting structure of the body, and site of inflammatory processes involved in rheumatic and other diseases.

Dr. Arnold R. Rich, Baxley Professor Emeritus of Pathology, Johns Hopkins University, Baltimore, for his major investigations into the allergic responses to drugs used in the treatment of certain rheumatic and other diseases.

Dr. John McMichael, Professor of Medicine, University of London, as the first man in England to apply the technique of cardiac catheterization and through this investigation to make a major contribution leading to the fuller diagnostic accuracy required in heart surgery.

Dr. Joshua H. Burn, retired Professor of Pharmacology, Oxford University, for outstanding contributions to knowledge of the action of drugs in cardiovascular disease.

The Gairdner Foundation was incorporated in 1957, and its funds are derived from personal gifts of Mr. Gairdner and his family. Mr. Gairdner was President of The Canadian Arthritis and Rheumatism Society from 1949 to 1952, and Chairman of its National Board of Directors from 1952 to 1958.

Mr. Gairdner said that the awards are prizes for achievements and not grants for the support of future research. Awards are intended to encourage and reward individuals who have made major contributions to the conquest of disease and human suffering, to help focus attention on the problems of arthritis and heart disease, and to facilitate communication of ideas among scientific workers in these fields.

Last year's award winners were: Dr. Alfred Blalock and Dr. Helen Taussig, of Baltimore; Dr. Harry Rose and Dr. Charles Ragan, of New York; Professor W. D. M. Paton and Professor Eleanor Zaimis, of Oxford and London, England, respectively, and Dr. W. G. Bigelow, of Toronto.

Applications for Charter Membership in The American Society of Diagnostic Radiology are now being received. Membership is open to cardiologists, chest physicians, gastroenterologists, rheumatologists, orthopedists, pediatricians, otolaryngologists, internists, and general practitioners *who do or may desire to do some types of diagnostic radiology in their offices.*

For further information write to Louis Shattuck Baer, M.D., Secretary, The American Society of Diagnostic Radiology, 411 Primrose Road, Burlingame, Calif.

The following statement by Leroy E. Burney, Surgeon General, U.S. Public Health Service, on INFLUENZA IMMUNIZATION is reproduced from *Public Health Reports*, Public Health Service, U.S. Department of Health, Education, and Welfare, Vol. 75, No. 10, p. 944, October, 1960:

Two outbreaks of influenza swept the United States in the fall of 1957 and the winter of 1958, resulting in 60,000 more deaths than would be expected under normal conditions. There were, in addition, more than 26,000 excess deaths during the first 3 months of 1960 which also were considered to be the result of influenza.

These departures from the usually predictable norms prompted the Surgeon General's Advisory Committee on Influenza Research to analyze the cause and to seek measures to prevent such an occurrence in the future.

The committee found that a new antigenic variant, the Asian strain, because of its widespread introduction and the general lack of resistance to it, was the direct cause of the excess number of deaths, not only in the total population but most markedly among the chronically ill, the aged, and pregnant women. As a result of these findings, the Public Health Service is urging a continuing program to protect these high-risk groups in order to prevent a recurrence of this excess mortality.

The high-risk groups who contribute most to the excess deaths and who the Public Health Service believes should be routinely immunized each year are:

1. Persons of all ages who suffer from chronic debilitating disease, in particular: (*a*) rheumatic heart disease, especially mitral stenosis; (*b*) other cardiovascular diseases, such as arteriosclerotic heart disease or hypertension—especially patients with evidence of frank or incipient insufficiency; (*c*) chronic bronchopulmonary disease, for example, chronic asthma, chronic bronchitis, bronchiectasis, pulmonary fibrosis, pulmonary emphysema, or pulmonary tuberculosis; (*d*) diabetes mellitus; (*e*) Addison's disease.

2. Pregnant women.

3. All persons 65 years or older.

The adult dosage recommended by the advisory committee for initial immunization is 1.0 cc. (500 cca units) of polyvalent vaccine, administered subcutaneously on two occasions separated by two or more months. Preferably, the first dose would be given no later than September 1 and the second no later than November 1. Persons previously immunized with polyvalent vaccine should be reinoculated with a single booster dose of 1.0 cc. subcutaneously each fall, prior to November 1. The only contraindication to vaccination would be a history of food allergy to eggs or chicken or a prior history of allergic reaction to an egg-produced vaccine, such as the commercial influenza product.

The time to start such a program is before the onset of the influenza season this fall. In the past, influenza vaccination has been sparse and sporadic, and primarily in response to an epidemic or the threat of an epidemic. The unpredictability of recurrence of influenza and its continued endemic occurrence are well known. Therefore, the Public Health Service strongly recommends that immunization of these high-risk groups be started now and continued annually, regardless of the predicted incidence of influenza for specific years.

The members of the Surgeon General's Advisory Committee on Influenza Research are: Colin M. MacLeod, M.D., chairman, University of Pennsylvania, Fred M. Davenport, M.D., University of Michigan, Morris Schaeffer, M.D., bureau of laboratories of the City of New York Health Department, George Burch, M.D., Tulane University, Dorland J. Davis, M.D., National Institute of Allergy and Infectious Diseases, Public Health Service, Thomas F. Sellers, M.D., Georgia State Department of Health, and Glenn S. Usher, M.D., Communicable Disease Center, Public Health Service.

Erratum

In the article entitled, "The Vectorcardiographic QRSsÊ-Loop Findings in Chronic Cor Pulmonale," by Thomas J. Walsh, M.D., Gonzalo T. Roman, Jr., M.D., and Edward Massie, M.D., which appeared in the October, 1960, issue of the Journal, the last sentence of the paragraph above Fig. 4 on page 603 should read: "It is of some interest that in only 2 of the 10 cases in the group with $R/S_{V1} > 1$ *was the amplitude of the R wave itself in this lead greater than 5 mm."*